SECTION V DRUGS THAT ACT IN THE CENTRAL NERVOUS SYSTEM

CHAPTER 21

Introduction to the Pharmacology of CNS Drugs

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Drugs acting in the central nervous system (CNS) were among the first to be discovered by primitive humans and are still the most widely used group of pharmacologic agents. In addition to their use in therapy, many drugs acting on the CNS are used without prescription to increase the sense of well-being.

The mechanisms by which various drugs act in the CNS have not always been clearly understood. In recent decades, however, dramatic advances have been made in the methodology of CNS pharmacology. It is now possible to study the action of a drug on individual cells and even single ion channels within synapses. The information obtained from such studies is the basis for several major developments in studies of the CNS.

First, it is clear that nearly all drugs with CNS effects act on specific receptors that modulate synaptic transmission. A very few agents such as general anesthetics and alcohol may have nonspecific actions on membranes (although these exceptions are not fully accepted), but even these non–receptor-mediated actions result in demonstrable alterations in synaptic transmission.

Second, drugs are among the most important tools for studying all aspects of CNS physiology, from the mechanism of convulsions to the laying down of long-term memory. As described below, agonists that mimic natural transmitters (and in many cases are more selective than the endogenous substances) and antagonists are extremely useful in such studies. The Box, Natural Toxins: Tools for Characterizing Ion Channels, describes a few of these substances.

Third, unraveling the actions of drugs with known clinical efficacy has led to some of the most fruitful hypotheses regarding the mechanisms of disease. For example, information about the action of antipsychotic drugs on dopamine receptors has provided the basis for important hypotheses regarding the pathophysiology of schizophrenia. Studies of the effects of a variety of agonists and antagonists on γ-aminobutyric acid (GABA) receptors have resulted in new concepts pertaining to the pathophysiology of several diseases, including anxiety and epilepsy.

This chapter provides an introduction to the functional organization of the CNS and its synaptic transmitters as a basis for understanding the actions of the drugs described in the following chapters.

Methods for the Study of CNS Pharmacology

Like many areas of science, major progress in the study of CNS drugs has depended on the development of new experimental techniques. The first detailed description of synaptic transmission

Natural Toxins: Tools For Characterizing Ion Channels

Evolution is tireless in the development of natural toxins. A vast number of variations are possible with even a small number of amino acids in peptides, and peptides make up only one of a broad array of toxic compounds. For example, the predatory marine snail genus *Conus* is estimated to include at least 500 different species. Each species kills or paralyzes its prey with a venom that contains 50–200 different peptides or proteins. Furthermore, there is little duplication of peptides among *Conus* species. Other animals with useful toxins include snakes, frogs, spiders, bees, wasps, and scorpions. Plant species with toxic (or therapeutic) substances are too numerous to mention here; they are referred to in many chapters of this book.

Since many toxins act on ion channels, they provide a wealth of chemical tools for studying the function of these channels. In fact, much of our current understanding of the properties of ion channels comes from studies utilizing only a small percentage of the highly potent and selective toxins that are now available. The toxins typically target voltage-sensitive ion channels, but a number of very useful toxins block ionotropic neurotransmitter receptors. Table 21–1 lists some of the toxins most commonly used in research, their mode of action, and their source.

TABLE 21–1 Some toxins used to characterize ion channels.

Channel Types	Mode of Toxin Action	Source
Voltage-gated		
Sodium channels		
Tetrodotoxin (TTX)	Blocks channel from outside	Puffer fish
Batrachotoxin (BTX)	Slows inactivation, shifts activation	Colombian frog
Potassium channels		
Apamin	Blocks "small Ca-activated" K channel	Honeybee
Charybdotoxin	Blocks "big Ca-activated" K channel	Scorpion
Calcium channels		
Omega conotoxin (ω-CTX-GVIA)	Blocks N-type channel	Pacific cone snail
Agatoxin (ω-AGAIVA)	Blocks P-type channel	Funnel web spider
Ligand-gated		
Nicotinic ACh receptor		
α-Bungarotoxin	Irreversible antagonist	Marine snake
$GABA_A$ receptor		
Picrotoxin	Blocks channel	South Pacific plant
Glycine receptor		
Strychnine	Competitive antagonist	Indian plant
AMPA receptor		
Philanthotoxin	Blocks channel	Wasp

was made possible by the invention of glass microelectrodes, which permit intracellular recording. The development of the brain slice technique permitted an analysis of the physiology and pharmacology of synapses. Detailed electrophysiologic studies of the action of drugs on both voltage- and transmitter-operated channels were further facilitated by the introduction of the patch clamp technique, which permits the recording of current through single channels. Channels can be expressed in cultured cells and the currents evoked by their activation recorded (Figure 21–1). Histochemical, immunologic, and radioisotopic methods have made it possible to map the distribution of specific transmitters, their associated enzyme systems, and their receptors. Molecular cloning has had a major impact on our understanding of CNS receptors. These techniques make it possible to determine the precise molecular structure of the receptors and their associated channels. Finally, mice with mutated genes for specific receptors or enzymes (knockout mice) can provide important information regarding the physiologic and pharmacologic roles of these components.

ION CHANNELS & NEUROTRANSMITTER RECEPTORS

The membranes of nerve cells contain two types of channels defined on the basis of the mechanisms controlling their gating (opening and closing): **voltage-gated** and **ligand-gated** channels (Figure 21–2A and B). Voltage-gated channels respond to changes in the membrane potential of the cell. The voltage-gated sodium channel described in Chapter 14 for the heart is an example of the first type of channel. In nerve cells, these channels are concentrated on the initial segment and the axon and are responsible for the fast action potential, which transmits the signal from cell body to nerve terminal. There are many types of voltage-sensitive calcium and potassium channels on the cell body, dendrites, and initial segment, which act on a much slower time scale and modulate the rate at which the neuron discharges. For example, some types of potassium channels opened by depolarization of the cell result in slowing of further depolarization and act as a brake to limit further action potential discharge.

Neurotransmitters exert their effects on neurons by binding to two distinct classes of receptor. The first class is referred to as **ligand-gated channels,** or **ionotropic receptors.** The receptor consists of subunits, and binding of ligand directly opens the channel, which is an integral parts of the receptor complex (see Figure 22–6). These channels are insensitive or only weakly sensitive to membrane potential. Activation of these channels typically

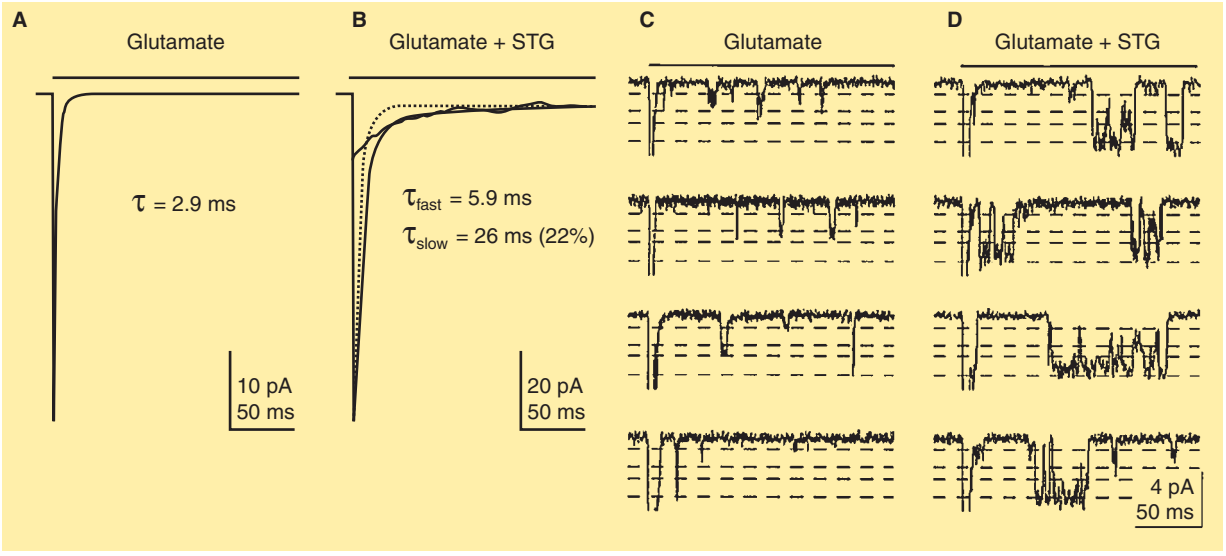

FIGURE 21–1 Whole-cell and single-channel currents. Modern techniques permit the recording of neuronal currents in response to the application of transmitters and modulators of transmission. **A:** Averaged and summed whole-cell currents evoked by the application of glutamate (inward currents are downward). **B:** Currents evoked by glutamate in the presence of a modulator (stargazin, STG). **C:** Single-channel currents evoked by glutamate alone. **D:** Single-channel currents evoked by glutamate plus stargazin. Note the prolonged channel openings in the presence of stargazin. (Reproduced, with permission, from Tomita et al: Stargazin modulates AMPA receptor gating and trafficking by distinct domains. Nature 2005;435:1052.)

results in a brief (a few milliseconds to tens of milliseconds) opening of the channel. Ligand-gated channels are responsible for fast synaptic transmission typical of hierarchical pathways in the CNS (see following text).

The second class of neurotransmitter receptor is referred to as **metabotropic receptors.** These are seven-transmembrane G protein-coupled receptors of the type described in Chapter 2. The binding of neurotransmitter to this type of receptor does not result in the direct gating of a channel. Rather, binding to the receptor engages a G protein, which results in the production of second messengers that modulate voltage-gated channels. These interactions can occur entirely with the plane of the membrane and are referred to as **membrane-delimited** pathways (Figure 21–2C). In this case, the G protein (often the βγ subunit) interacts directly with the voltage-gated ion channel. In general, two types of voltage-gated ion channels are the targets of this type of signaling: calcium channels and potassium channels. When G proteins interact with calcium channels, they inhibit channel function. This mechanism accounts for the presynaptic inhibition that occurs when presynaptic metabotropic receptors are activated. In contrast, when these receptors are postsynaptic, they activate (cause the opening of) potassium channels, resulting in a slow postsynaptic inhibition. Metabotropic receptors can also modulate voltage-gated channels less directly by the generation of **diffusible second messengers** (Figure 21–2D). A classic example of this type of action is provided by the β adrenoceptor, which generates cAMP via the activation of adenylyl cyclase (see Chapter 2). Whereas membrane-delimited actions occur within microdomains in the membrane, second messenger-mediated effects can occur over considerable distances. Finally, an important consequence of the involvement of G proteins in receptor signaling is that, in contrast to the brief effect of ionotropic receptors, the effects of metabotropic receptor activation can last tens of seconds to minutes. Metabotropic receptors predominate in the diffuse neuronal systems in the CNS (see below).

THE SYNAPSE & SYNAPTIC POTENTIALS

The communication between neurons in the CNS occurs through chemical synapses in the majority of cases. (A few instances of electrical coupling between neurons have been documented, and such coupling may play a role in synchronizing neuronal discharge. However, it is unlikely that these electrical synapses are an important site of drug action.) The events involved in synaptic transmission can be summarized as follows.

An action potential in the presynaptic fiber propagates into the synaptic terminal and activates voltage-sensitive calcium channels in the membrane of the terminal (see Figure 6–3). The calcium channels responsible for the release of transmitter are generally resistant to the calcium channel-blocking agents discussed in Chapter 12 (verapamil, etc) but are sensitive to blockade by certain marine toxins and metal ions (see Tables 21–1 and 12–4). Calcium flows into the terminal, and the increase in intraterminal calcium concentration promotes the fusion of synaptic vesicles with the presynaptic membrane. The transmitter contained in the vesicles is released into the synaptic cleft and diffuses to the receptors on the postsynaptic membrane. Binding of the transmitter to its receptor causes a brief change in membrane conductance (permeability to ions) of the postsynaptic cell. The time delay from the arrival of the presynaptic action potential to the onset of the postsynaptic response is approximately

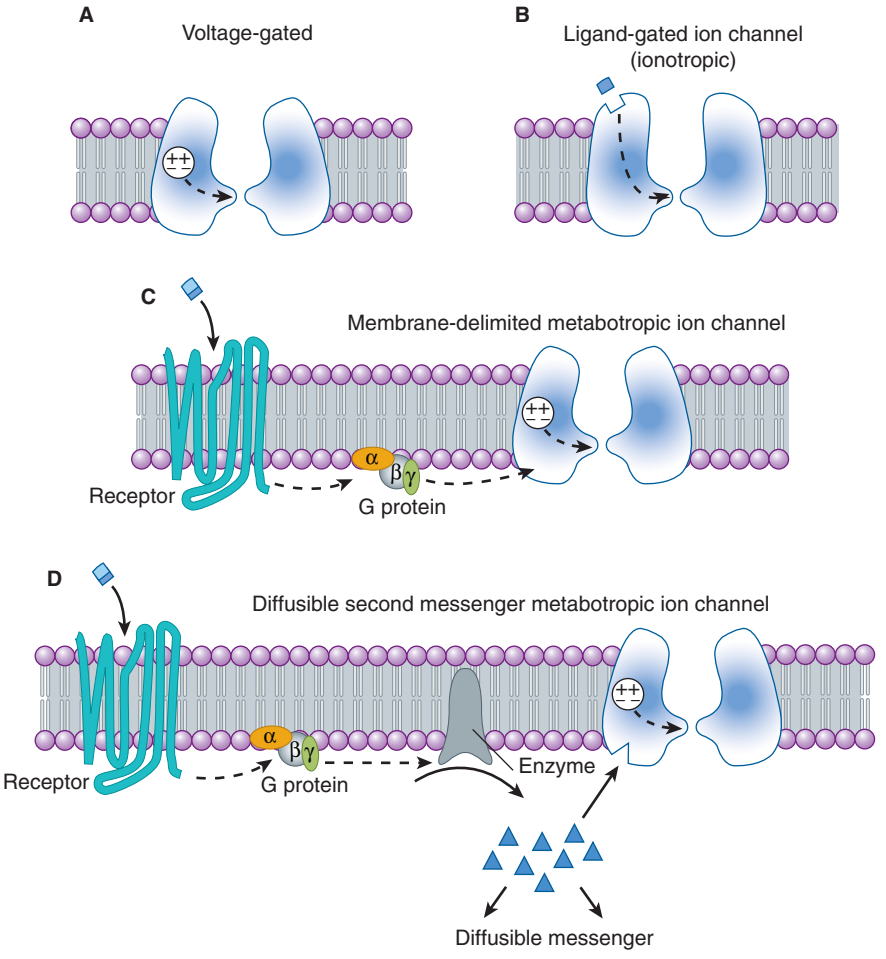

FIGURE 21–2 Types of ion channels and neurotransmitter receptors in the CNS. **A** shows a voltage-gated channel in which a voltage sensor component of the protein controls the gating (*broken arrow*) of the channel. **B** shows a ligand-gated channel in which the binding of the neurotransmitter to the ionotropic channel receptor controls the gating (*broken arrow*) of the channel. **C** shows a G protein-coupled (metabotropic) receptor, which, when bound, activates a G protein that then interacts directly to modulate an ion channel. **D** shows a G protein-coupled receptor, which, when bound, activates a G protein that then activates an enzyme. The activated enzyme generates a diffusible second messenger, eg, cAMP, which interacts to modulate an ion channel.

0.5 ms. Most of this delay is consumed by the release process, particularly the time required for calcium channels to open.

The first systematic analysis of synaptic potentials in the CNS was in the early 1950s by Eccles and associates, who recorded intracellularly from spinal motor neurons. When a microelectrode enters a cell, there is a sudden change in the potential recorded by the electrode, which is typically about –70 mV (Figure 21–3). This is the resting membrane potential of the neuron. Two types of pathways—excitatory and inhibitory—impinge on the motor neuron.

When an excitatory pathway is stimulated, a small depolarization or **excitatory postsynaptic potential (EPSP)** is recorded. This potential is due to the excitatory transmitter acting on an ionotropic receptor, causing an increase in cation permeability. Changing the stimulus intensity to the pathway, and therefore the number of presynaptic fibers activated, results in a graded change in the size of the depolarization. When a sufficient number of excitatory fibers are activated, the excitatory postsynaptic potential

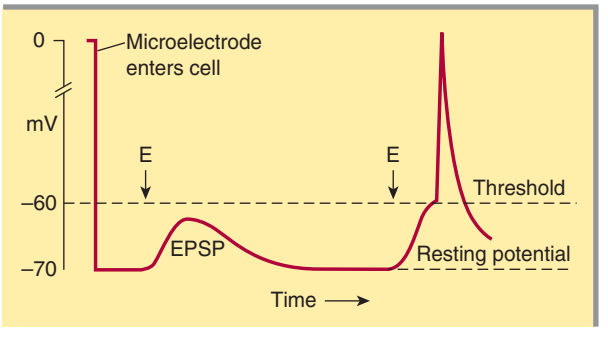

FIGURE 21–3 Excitatory postsynaptic potentials (EPSP) and spike generation. The figure shows entry of a microelectrode into a postsynaptic cell and subsequent recording of a resting membrane potential of –70 mV. Stimulation of an excitatory pathway (E) generates transient depolarization. Increasing the stimulus strength (second E) increases the size of the depolarization, so that the threshold for spike generation is reached.

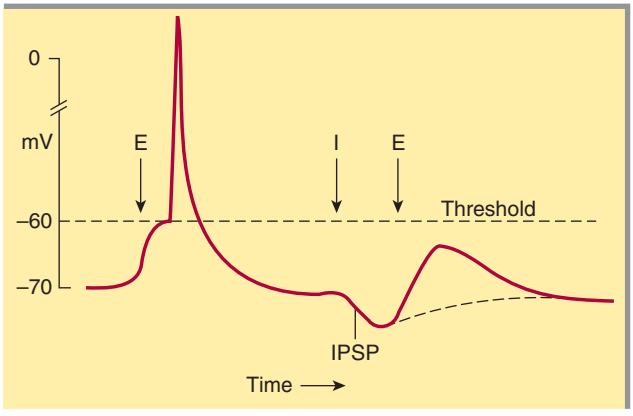

FIGURE 21–4 Interaction of excitatory and inhibitory synapses. On the left, a suprathreshold stimulus is given to an excitatory pathway (E) and an action potential is evoked. On the right, this same stimulus is given shortly after activating an inhibitory pathway (I), which results in an inhibitory postsynaptic potential (IPSP) that prevents the excitatory potential from reaching threshold.

depolarizes the postsynaptic cell to threshold, and an all-or-none action potential is generated.

When an inhibitory pathway is stimulated, the postsynaptic membrane is hyperpolarized owing to the selective opening of chloride channels, producing an **inhibitory postsynaptic potential (IPSP)** (Figure 21–4). However, because the equilibrium potential for chloride is only slightly more negative than the resting potential (~ –65 mV), the hyperpolarization is small and contributes only modestly to the inhibitory action. The opening of the chloride channel during the inhibitory postsynaptic potential makes the neuron "leaky" so that changes in membrane potential are more difficult to achieve. This shunting effect decreases the change in membrane potential during the excitatory postsynaptic potential. As a result, an excitatory postsynaptic potential that evoked an action potential under resting conditions fails to evoke an action potential during the inhibitory postsynaptic potential (Figure 21–4). A second type of inhibition is **presynaptic inhibition.** It was first described for sensory fibers entering the spinal cord, where excitatory synaptic terminals receive synapses called axoaxonic synapses (described later). When activated, axoaxonic synapses reduce the amount of transmitter released from the terminals of sensory fibers. It is interesting that presynaptic inhibitory receptors are present on almost all presynaptic terminals in the brain even though axoaxonic synapses appear to be restricted to the spinal cord. In the brain, transmitter spills over to neighboring synapses to activate the presynaptic receptors.

SITES OF DRUG ACTION

Virtually all the drugs that act in the CNS produce their effects by modifying some step in chemical synaptic transmission. Figure 21–5 illustrates some of the steps that can be altered. These transmitter-dependent actions can be divided into presynaptic and postsynaptic categories.

Drugs acting on the synthesis, storage, metabolism, and release of neurotransmitters fall into the presynaptic category. Synaptic transmission can be depressed by blockade of transmitter synthesis or storage. For example, reserpine depletes monoamine synapses of transmitters by interfering with intracellular storage. Blockade of transmitter catabolism inside the nerve terminal can increase transmitter concentrations and has been reported to increase the amount of transmitter released per impulse. Drugs can also alter the release of transmitters. The stimulant amphetamine induces the release of catecholamines from adrenergic synapses (see Chapters 6 and 32). Capsaicin causes the release of the peptide substance P from sensory neurons, and tetanus toxin blocks the release of transmitters. After a transmitter has been released into the synaptic cleft, its action is terminated either by uptake or by degradation. For most neurotransmitters, there are uptake mechanisms into the synaptic terminal and also into surrounding neuroglia. Cocaine, for example, blocks the uptake of catecholamines at adrenergic synapses and thus potentiates the action of these amines. However, acetylcholine is inactivated by enzymatic degradation, not reuptake. Anticholinesterases block the degradation of acetylcholine and thereby prolong its action. No uptake mechanism has been found for any of the numerous CNS peptides, and it has yet to be demonstrated whether specific enzymatic degradation terminates the action of peptide transmitters.

In the postsynaptic region, the transmitter receptor provides the primary site of drug action. Drugs can act either as neurotransmitter agonists, such as the opioids, which mimic the action of enkephalin, or they can block receptor function. Receptor antagonism is a common mechanism of action for CNS drugs. An example is strychnine's blockade of the receptor for the inhibitory transmitter glycine. This block, which underlies strychnine's convulsant action, illustrates how the blockade of inhibitory processes results in excitation. Drugs can also act directly on the ion channel of ionotropic receptors. For example, barbiturates can enter and block the channel of many excitatory ionotropic receptors. In the case of metabotropic receptors, drugs can act at any of the steps downstream of the receptor. Perhaps the best example is provided by the methylxanthines, which can modify neurotransmitter responses mediated through the second-messenger cAMP. At high concentrations, the methylxanthines elevate the level of cAMP by blocking its metabolism and thereby prolong its action.

The traditional view of the synapse is that it functions like a valve, transmitting information in one direction. However, it is now clear that the synapse can generate signals that feed back onto the presynaptic terminal to modify transmitter release. Endocannabinoids are the best documented example of such *retrograde* signaling. Postsynaptic activity leads to the synthesis and release of endocannabinoids, which then bind to receptors on the presynaptic terminal. Although the gas nitric oxide (NO) has long been proposed as a retrograde messenger, its physiologic role in the CNS is still not well understood.

The selectivity of CNS drug action is based almost entirely on the fact that different transmitters are used by different groups of

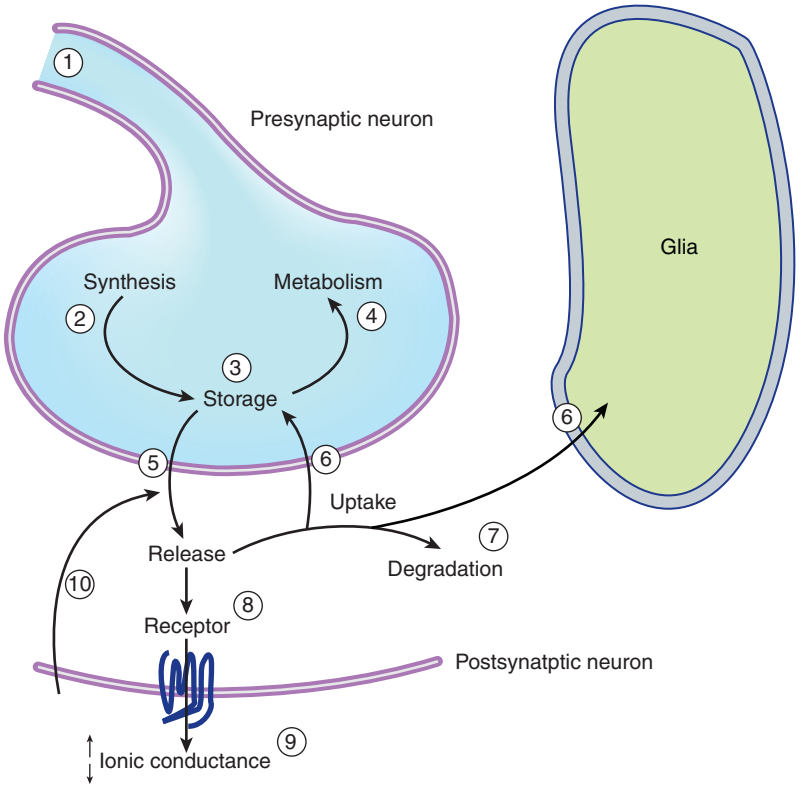

FIGURE 21–5 Sites of drug action. Schematic drawing of steps at which drugs can alter synaptic transmission. (1) Action potential in presynaptic fiber; (2) synthesis of transmitter; (3) storage; (4) metabolism; (5) release; (6) reuptake into the nerve ending or uptake into a glial cell; (7) degradation; (8) receptor for the transmitter; (9) receptor-induced increase or decrease in ionic conductance; (10) retrograde signaling.

neurons. Furthermore, these transmitters are often segregated into neuronal systems that subserve broadly different CNS functions. Without such segregation, it would be impossible to selectively modify CNS function, even if one had a drug that operated on a single neurotransmitter system. That such segregation does occur has provided neuroscientists with a powerful pharmacologic approach for analyzing CNS function and treating pathologic conditions.

IDENTIFICATION OF CENTRAL NEUROTRANSMITTERS

Because drug selectivity is based on the fact that different pathways use different transmitters, a primary goal of neuropharmacologists is to identify the transmitters in CNS pathways. Establishing that a chemical substance is a transmitter has been far more difficult for central synapses than for peripheral synapses. The following criteria have been established for transmitter identification.

Localization

Approaches that have been used to prove that a suspected transmitter resides in the presynaptic terminal of the pathway under study include biochemical analysis of regional concentrations of suspected transmitters and immunocytochemical techniques for enzymes and peptides.

Release

To determine whether the substance is released from a particular region, local collection (in vivo) of the extracellular fluid can sometimes be accomplished. In addition, slices of brain tissue can be electrically or chemically stimulated in vitro and the released substances measured. To determine whether the release is relevant to synaptic transmission, it is important to establish that the release is calcium-dependent.

Synaptic Mimicry

Finally, application of the suspected substance should produce a response that mimics the action of the transmitter released by nerve stimulation. Furthermore, application of a selective antagonist should block the response. Micro-iontophoresis, which permits highly localized drug administration, has been a valuable technique in assessing the action of suspected transmitters. Because of the complexity of the CNS, specific pharmacologic antagonism of a synaptic response provides a particularly powerful technique for transmitter identification.

CELLULAR ORGANIZATION OF THE BRAIN

Most of the neuronal systems in the CNS can be divided into two broad categories: **hierarchical** systems and **nonspecific** or **diffuse** neuronal systems.

Hierarchical Systems

Hierarchical systems include all the pathways directly involved in sensory perception and motor control. The pathways are generally clearly delineated, being composed of large myelinated fibers that can often conduct action potentials at a rate of more than 50 m/s. The information is typically phasic and occurs in bursts of action potentials. In sensory systems, the information is processed sequentially by successive integrations at each relay nucleus on its way to the cortex. A lesion at any link incapacitates the system. Within each nucleus and in the cortex, there are two types of cells: **relay** or **projection neurons** and **local circuit neurons** (Figure 21–6A). The projection neurons that form the interconnecting pathways transmit signals over long distances. The cell bodies are relatively large, and their axons emit collaterals that arborize extensively in the vicinity of the neuron. These neurons are excitatory, and their synaptic influences, which involve ionotropic receptors, are very short-lived.

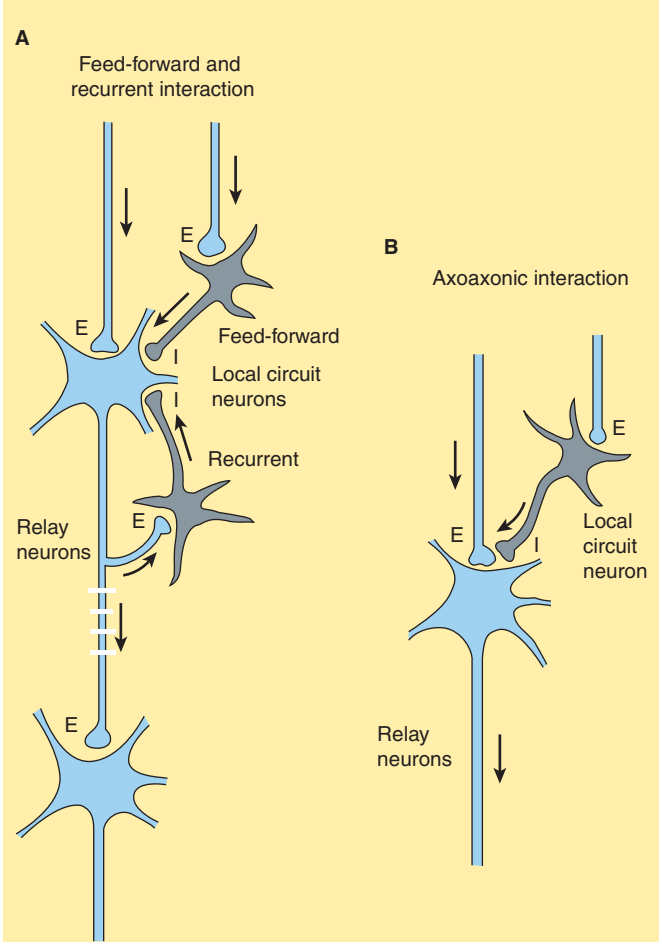

FIGURE 21–6 Pathways in the central nervous system. **A** shows parts of three relay neurons (blue) and two types of inhibitory pathways, recurrent and feed-forward. The inhibitory neurons are shown in gray. **B** shows the pathway responsible for presynaptic inhibition in which the axon of an inhibitory neuron (gray) synapses on the axon terminal of an excitatory fiber (blue).

The excitatory transmitter released from these cells is, in most instances, **glutamate.** Local circuit neurons are typically smaller than projection neurons, and their axons arborize in the immediate vicinity of the cell body. Most of these neurons are inhibitory, and they release either **GABA** or **glycine.** They synapse primarily on the cell body of the projection neurons but can also synapse on the dendrites of projection neurons as well as with each other. Two common types of pathways for these neurons (Figure 21–6A) include recurrent feedback pathways and feed-forward pathways. A special class of local circuit neurons in the spinal cord forms axoaxonic synapses on the terminals of sensory axons (Figure 21–6B). In some sensory pathways such as the retina and olfactory bulb, local circuit neurons may actually lack an axon and release neurotransmitter from dendritic synapses in a graded fashion in the absence of action potentials.

Although there is a great variety of synaptic connections in these hierarchical systems, the fact that a limited number of transmitters are used by these neurons indicates that any major pharmacologic manipulation of this system will have a profound effect on the overall excitability of the CNS. For instance, selectively blocking $GABA_A$ receptors with a drug such as picrotoxin results in generalized convulsions. Thus, although the mechanism of action of picrotoxin is specific in blocking the effects of GABA, the overall functional effect appears to be quite nonspecific, because GABA-mediated synaptic inhibition is so widely utilized in the brain.

Nonspecific or Diffuse Neuronal Systems

Neuronal systems that contain one of the monoamines—norepinephrine, dopamine, or 5-hydroxytryptamine (serotonin)—provide examples in this category. Certain other pathways emanating from the reticular formation and possibly some peptide-containing pathways also fall into this category. These systems differ in fundamental ways from the hierarchical systems, and the noradrenergic systems serve to illustrate the differences.

Noradrenergic cell bodies are found primarily in a compact cell group called the locus caeruleus located in the caudal pontine central gray matter. The number of neurons in this cell group is small, approximately 1500 on each side of the brain in the rat.

Because these axons are fine and unmyelinated, they conduct very slowly, at about 0.5 m/s. The axons branch repeatedly and are extraordinarily divergent. Branches from the same neuron can innervate several functionally different parts of the CNS. In the neocortex, these fibers have a tangential organization and therefore can monosynaptically influence large areas of cortex. The pattern of innervation by noradrenergic fibers in the cortex and nuclei of the hierarchical systems is diffuse, and these fibers form a very small percentage of the total number in the area. In addition, the axons are studded with periodic enlargements called varicosities, which contain large numbers of vesicles. In some instances, these varicosities do not form synaptic contacts, suggesting that norepinephrine may be released in a rather diffuse manner, as occurs with the noradrenergic autonomic innervation of smooth muscle. This indicates that the cellular targets of these

systems are determined largely by the location of the receptors rather than by the location of the release sites. Finally, most neurotransmitters utilized by diffuse neuronal systems, including norepinephrine, act—perhaps exclusively—on metabotropic receptors and therefore initiate long-lasting synaptic effects. Based on these observations, it is clear that the monoamine systems cannot be conveying topographically specific types of information; rather, vast areas of the CNS must be affected simultaneously and in a rather uniform way. It is not surprising, then, that these systems have been implicated in such global functions as sleeping and waking, attention, appetite, and emotional states.

CENTRAL NEUROTRANSMITTERS

A vast number of small molecules have been isolated from the brain, and studies using a variety of approaches suggest that the agents listed in Table 21–2 are neurotransmitters. A brief summary of the evidence for some of these compounds follows.

Amino Acids

The amino acids of primary interest to the pharmacologist fall into two categories: the acidic amino acid glutamate and the neutral amino acids glycine and GABA. All these compounds are

TABLE 21–2 Summary of neurotransmitter pharmacology in the central nervous system.

Transmitter	Anatomy	Receptor Subtypes and Preferred Agonists	Receptor Antagonists	Mechanisms
Acetylcholine	Cell bodies at all levels; long and short connections	Muscarinic (M_1): muscarine	Pirenzepine, atropine	Excitatory: ↓ in K^+ conductance; ↑ IP_3, DAG
		Muscarinic (M_2): muscarine, bethanechol	Atropine, methoctramine	Inhibitory: ↑ K^+ conductance; ↓ cAMP
	Motoneuron-Renshaw cell synapse	Nicotinic: nicotine	Dihydro-β-erythroidine, α-bungarotoxin	Excitatory: ↑ cation conductance
Dopamine	Cell bodies at all levels; short, medium, and long connections	D_1	Phenothiazines	Inhibitory (?): ↑ cAMP
		D_2: bromocriptine	Phenothiazines, butyrophenones	Inhibitory (presynaptic): ↓ Ca^{2+}; Inhibitory (postsynaptic): ↑ in K^+ conductance, ↓ cAMP
GABA	Supraspinal and spinal interneurons involved in pre- and postsynaptic inhibition	$GABA_A$: muscimol	Bicuculline, picrotoxin	Inhibitory: ↑ Cl^- conductance
		$GABA_B$: baclofen	2-OH saclofen	Inhibitory (presynaptic): ↓ Ca^{2+} conductance; Inhibitory (postsynaptic): ↑ K^+ conductance
Glutamate	Relay neurons at all levels and some interneurons	*N*-Methyl-D-aspartate (NMDA): NMDA	2-Amino-5-phosphonovalerate, dizocilpine	Excitatory: ↑ cation conductance, particularly Ca^{2+}
		AMPA: AMPA	CNQX	Excitatory: ↑ cation conductance
		Kainate: kainic acid, domoic acid		
		Metabotropic: ACPD, quisqualate	MCPG	Inhibitory (presynaptic): ↓ Ca^{2+} conductance, ↓ cAMP; Excitatory: ↓ K^+ conductance, ↑ IP_3, DAG
Glycine	Spinal interneurons and some brainstem interneurons	Taurine, β-alanine	Strychnine	Inhibitory: ↑ Cl^- conductance
5-Hydroxytryptamine (serotonin)	Cell bodies in midbrain and pons project to all levels	$5\text{-}HT_{1A}$: LSD	Metergoline, spiperone	Inhibitory: ↑ K^+ conductance, ↓ cAMP
		$5\text{-}HT_{2A}$: LSD	Ketanserin	Excitatory: ↓ K^+ conductance, ↑ IP_3, DAG

(*continued*)

TABLE 21–2 Summary of neurotransmitter pharmacology in the central nervous system. (Continued)

Transmitter	Anatomy	Receptor Subtypes and Preferred Agonists	Receptor Antagonists	Mechanisms
		5-HT_3: 2-methyl-5-HT	Ondansetron	Excitatory: ↑ cation conductance
		5-HT_4		Excitatory: ↓ K^+ conductance
Norepinephrine	Cell bodies in pons and brainstem project to all levels	α_1: phenylephrine	Prazosin	Excitatory: ↓ K^+ conductance, ↑ IP_3, DAG
		α_2: clonidine	Yohimbine	Inhibitory (presynaptic): ↓ Ca^{2+} conductance; Inhibitory: ↑ K^+ conductance, ↓ cAMP
		β_1: isoproterenol, dobutamine	Atenolol, practolol	Excitatory: ↓ K^+ conductance, ↑ cAMP
		β_2: albuterol	Butoxamine	Inhibitory: may involve ↑ in electrogenic sodium pump; ↑ cAMP
Histamine	Cells in ventral posterior hypothalamus	H_1: 2(*m*-fluorophenyl)-histamine	Mepyramine	Excitatory: ↓ K^+ conductance, ↑ IP_3, DAG
		H_2: dimaprit	Ranitidine	Excitatory: ↓ K^+ conductance, ↑ cAMP
		H_3: *R*-α-methyl-histamine	Thioperamide	Inhibitory autoreceptors
Opioid peptides	Cell bodies at all levels; long and short connections	Mu: bendorphin	Naloxone	Inhibitory (presynaptic): ↓ Ca^{2+} conductance, ↓ cAMP
		Delta: enkephalin	Naloxone	Inhibitory (postsynaptic): ↑ K^+ conductance, ↓ cAMP
		Kappa: dynorphin	Naloxone	
Tachykinins	Primary sensory neurons, cell bodies at all levels; long and short connections	NK1: substance P methylester, aprepitant	Aprepitant	Excitatory: ↓ K^+ conductance, ↑ IP_3, DAG
		NK2		
		NK3		
Endocannabinoids	Widely distributed	CB1: anandamide, 2-arachidonyglycerol	Rimonabant	Inhibitory (presynaptic): ↓ Ca^{2+} conductance, ↓ cAMP

Note: Many other central transmitters have been identified (see text).

ACPD, *trans*-1-amino-cyclopentyl-1,3-dicarboxylate; AMPA, DL-α-amino-3-hydroxy-5-methylisoxazole-4-propionate; cAMP, cyclic adenosine monophosphate; CQNX, 6-cyano-7-nitroquinoxaline-2,3-dione; DAG, diacylglycerol; IP_3, inositol trisphosphate; LSD, lysergic acid diethylamide; MCPG, α-methyl-4-carboxyphenylglycine.

present in high concentrations in the CNS and are extremely potent modifiers of neuronal excitability.

A. Glutamate

Excitatory synaptic transmission is mediated by glutamate, which is present in very high concentrations in excitatory synaptic vesicles (~100 mM). Glutamate is released into the synaptic cleft by Ca^{2+}-dependent exocytosis (Figure 21–7). The released glutamate acts on postsynaptic glutamate receptors and is cleared by glutamate transporters present on surrounding glia. In glia, glutamate is converted to glutamine by glutamine synthetase, released from the glia, taken up by the nerve terminal, and converted back to glutamate by the enzyme glutaminase. The high concentration of glutamate in synaptic vesicles is achieved by the **vesicular glutamate transporter (VGLUT).**

Almost all neurons that have been tested are strongly excited by glutamate. This excitation is caused by the activation of both ionotropic and metabotropic receptors, which have been extensively characterized by molecular cloning. The ionotropic receptors can be further divided into three subtypes based on the action of selective agonists: α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid **(AMPA),** kainic acid **(KA),** and *N*-methyl-D-aspartate

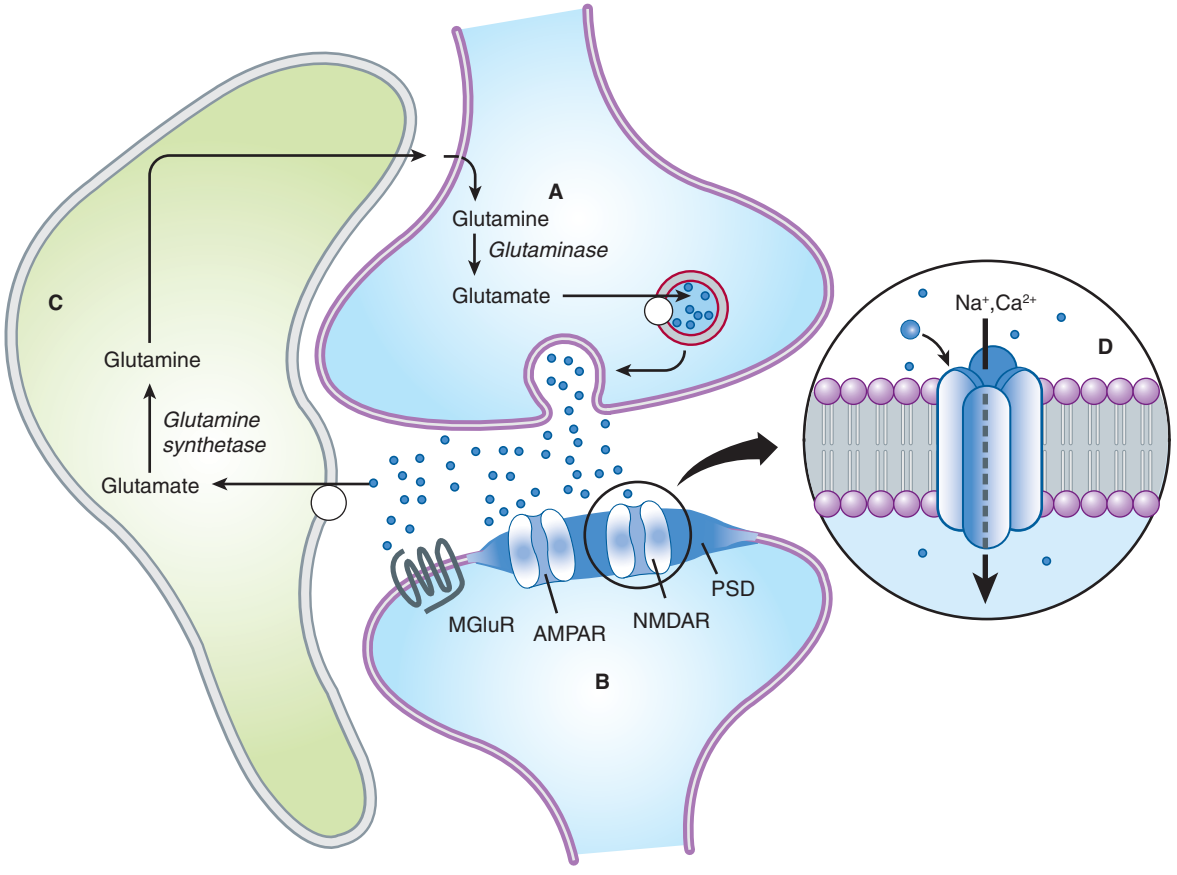

FIGURE 21–7 Schematic diagram of a glutamate synapse. Glutamine is imported into the glutamatergic neuron **(A)** and converted into glutamate by glutaminase. The glutamate is then concentrated in vesicles by the vesicular glutamate transporter. Upon release into the synapse, glutamate can interact with AMPA and NMDA ionotropic receptor channels (AMPAR, NMDAR) in the postsynaptic density (PSD) and with metabotropic receptors (MGluR) on the postsynaptic cell **(B)**. Synaptic transmission is terminated by active transport of the glutamate into a neighboring glial cell **(C)** by a glutamate transporter. It is synthesized into glutamine by glutamine synthetase and exported into the glutamatergic axon. **(D)** shows a model NMDA receptor channel complex consisting of a tetrameric protein that becomes permeable to Na^+ and Ca^{2+} when it binds a glutamate molecule.

(NMDA). All the ionotropic receptors are composed of four subunits. AMPA receptors, which are present on all neurons, are heterotetramers assembled from four subunits (GluA1–GluA4). The majority of AMPA receptors contain the GluA2 subunit and are permeable to Na^+ and K^+, but not to Ca^{2+}. Some AMPA receptors, typically present on inhibitory interneurons, lack the GluA2 subunit and are also permeable to Ca^{2+}.

Kainate receptors are not as uniformly distributed as AMPA receptors, being expressed at high levels in the hippocampus, cerebellum, and spinal cord. They are formed from a number of subunit combinations (GluK1–GluK5). Although GluK4 and GluK5 are unable to form channels on their own, their presence in the receptor changes the receptor's affinity and kinetics. Similar to AMPA receptors, kainate receptors are permeable to Na^+ and K^+ and in some subunit combinations can also be permeable to Ca^{2+}.

NMDA receptors are as ubiquitous as AMPA receptors, being present on essentially all neurons in the CNS. All NMDA receptors require the presence of the subunit GluN1. The channel also contains one or two NR2 subunits (GluN2A–GluN2D). Unlike AMPA and kainate receptors, all NMDA receptors are highly permeable to Ca^{2+} as well as to Na^+ and K^+. NMDA receptor function is controlled in a number of intriguing ways. In addition to glutamate binding, the channel also requires the binding of glycine to a separate site. The physiologic role of glycine binding is unclear because the glycine site appears to be saturated at normal ambient levels of glycine. Another key difference between AMPA and kainate receptors on the one hand, and NMDA receptors on the other, is that AMPA and kainate receptor activation results in channel opening at resting membrane potential, whereas NMDA receptor activation does not. This is due to the voltage-dependent block of the NMDA pore by extracellular Mg^{2+}. When the neuron is strongly depolarized, as occurs with intense activation of the synapse or by activation of neighboring synapses, Mg^{2+} is expelled and the channel opens. Thus, there are two requirements for NMDA receptor channel opening: Glutamate must bind the receptor and the membrane must be depolarized. The rise in intracellular Ca^{2+} that accompanies channel opening results in a long-lasting enhancement in synaptic strength that is referred

to as **long-term potentiation (LTP).** The change can last for many hours or even days and is generally accepted as an important cellular mechanism underlying learning and memory.

The metabotropic glutamate receptors are G protein-coupled receptors that act indirectly on ion channels via G proteins. Metabotropic receptors (mGluR1–mGluR8) have been divided into three groups (I, II, and III). A variety of agonists and antagonists have been developed that interact selectively with the different groups. Group I receptors are typically located postsynaptically and are thought to cause neuronal excitation by activating a nonselective cation channel. These receptors also activate phospholipase C, leading to inositol trisphosphate-mediated intracellular Ca^{2+} release. In contrast, group II and group III receptors are typically located on presynaptic nerve terminals and act as inhibitory autoreceptors. Activation of these receptors causes the inhibition of Ca^{2+} channels, resulting in inhibition of transmitter release. These receptors are activated only when the concentration of glutamate rises to high levels during repetitive stimulation of the synapse. Activation of these receptors causes the inhibition of adenylyl cyclase and decreases cAMP generation.

The postsynaptic membrane at excitatory synapses is thickened and referred to as the **postsynaptic density** (PSD; Figure 21–7). This is a highly complex structure containing glutamate receptors, signaling proteins, scaffolding proteins, and cytoskeletal proteins. A typical excitatory synapse contains AMPA receptors, which tend to be located toward the periphery, and NMDA receptors, which are concentrated in the center. Kainate receptors are present at a subset of excitatory synapses, but their exact location is unknown. Metabotropic glutamate receptors (group I), which are localized just outside the postsynaptic density, are also present at some excitatory synapses.

B. GABA and Glycine

Both GABA and glycine are inhibitory neurotransmitters, which are typically released from local interneurons. Interneurons that release glycine are restricted to the spinal cord and brainstem, whereas interneurons releasing GABA are present throughout the CNS, including the spinal cord. It is interesting that some interneurons in the spinal cord can release both GABA and glycine. Glycine receptors are pentameric structures that are selectively permeable to Cl^-. Strychnine, which is a potent spinal cord convulsant and has been used in some rat poisons, selectively blocks glycine receptors.

GABA receptors are divided into two main types: $GABA_A$ and $GABA_B$. Inhibitory postsynaptic potentials in many areas of the brain have a fast and slow component. The fast component is mediated by $GABA_A$ receptors and the slow component by $GABA_B$ receptors. The difference in kinetics stems from the differences in coupling of the receptors to ion channels. $GABA_A$ receptors are ionotropic receptors and, like glycine receptors, are pentameric structures that are selectively permeable to Cl^-. These receptors are selectively inhibited by picrotoxin and bicuculline, both of which cause generalized convulsions. A great many subunits for $GABA_A$ receptors have been cloned; this accounts for the large diversity in the pharmacology of $GABA_A$ receptors, making them key targets for clinically useful agents (see Chapter 22). $GABA_B$ receptors are metabotropic receptors that are selectively activated by the antispastic drug baclofen. These receptors are coupled to G proteins that, depending on their cellular location, either inhibit Ca^{2+} channels or activate K^+ channels. The $GABA_B$ component of the inhibitory postsynaptic potential is due to a selective increase in K^+ conductance. This inhibitory postsynaptic potential is long-lasting and slow because the coupling of receptor activation to K^+ channel opening is indirect and delayed. $GABA_B$ receptors are localized to the perisynaptic region and thus require the spillover of GABA from the synaptic cleft. $GABA_B$ receptors are also present on the axon terminals of many excitatory and inhibitory synapses. In this case, GABA spills over onto these presynaptic $GABA_B$ receptors, inhibiting transmitter release by inhibiting Ca^{2+} channels. In addition to their coupling to ion channels, $GABA_B$ receptors also inhibit adenylyl cyclase and decrease cAMP generation.

Acetylcholine

Acetylcholine was the first compound to be identified pharmacologically as a transmitter in the CNS. Eccles showed in the early 1950s that excitation of Renshaw cells by motor axon collaterals in the spinal cord was blocked by nicotinic antagonists. Furthermore, Renshaw cells were extremely sensitive to nicotinic agonists. These experiments were remarkable for two reasons. First, this early success at identifying a transmitter for a central synapse was followed by disappointment because it remained the sole central synapse for which the transmitter was known until the late 1960s, when comparable data became available for GABA and glycine. Second, the motor axon collateral synapse remains one of the best-documented examples of a cholinergic nicotinic synapse in the mammalian CNS, despite the rather widespread distribution of nicotinic receptors as defined by in situ hybridization studies. Most CNS responses to acetylcholine are mediated by a large family of G protein-coupled muscarinic receptors. At a few sites, acetylcholine causes slow inhibition of the neuron by activating the M_2 subtype of receptor, which opens potassium channels. A far more widespread muscarinic action in response to acetylcholine is a slow excitation that in some cases is mediated by M_1 receptors. These muscarinic effects are much slower than either nicotinic effects on Renshaw cells or the effect of amino acids. Furthermore, this M_1 muscarinic excitation is unusual in that acetylcholine produces it by *decreasing* the membrane permeability to potassium, ie, the opposite of conventional transmitter action.

A number of pathways contain acetylcholine, including neurons in the neostriatum, the medial septal nucleus, and the reticular formation. Cholinergic pathways appear to play an important role in cognitive functions, especially memory. Presenile dementia of the Alzheimer type is reportedly associated with a profound loss of cholinergic neurons. However, the specificity of this loss has been questioned because the levels of other putative transmitters, eg, somatostatin, are also decreased.

Monoamines

Monoamines include the catecholamines (dopamine and norepinephrine) and 5-hydroxytryptamine. Although these compounds are present in very small amounts in the CNS, they can be localized using extremely sensitive histochemical methods. These pathways are the site of action of many drugs; for example, the CNS stimulants cocaine and amphetamine appear to act primarily at catecholamine synapses. Cocaine blocks the reuptake of dopamine and norepinephrine, whereas amphetamines cause presynaptic terminals to release these transmitters.

A. Dopamine

The major pathways containing dopamine are the projection linking the substantia nigra to the neostriatum and the projection linking the ventral tegmental region to limbic structures, particularly the limbic cortex. The therapeutic action of the antiparkinsonism drug levodopa is associated with the former area (see Chapter 28), whereas the therapeutic action of the antipsychotic drugs is thought to be associated with the latter (see Chapter 29). Dopamine-containing neurons in the tuberobasal ventral hypothalamus play an important role in regulating hypothalamohypophysial function. Five dopamine receptors have been identified, and they fall into two categories: D_1-like (D_1 and D_5) and D_2-like (D_2, D_3, D_4). All dopamine receptors are metabotropic. Dopamine generally exerts a slow inhibitory action on CNS neurons. This action has been best characterized on dopamine-containing substantia nigra neurons, where D_2-receptor activation opens potassium channels via the G_i coupling protein.

B. Norepinephrine

Most noradrenergic neurons are located in the locus caeruleus or the lateral tegmental area of the reticular formation. Although the density of fibers innervating various sites differs considerably, most regions of the CNS receive diffuse noradrenergic input. All noradrenergic receptor subtypes are metabotropic. When applied to neurons, norepinephrine can hyperpolarize them by increasing potassium conductance. This effect is mediated by α_2 receptors and has been characterized most thoroughly on locus caeruleus neurons. In many regions of the CNS, norepinephrine actually enhances excitatory inputs by both indirect and direct mechanisms. The indirect mechanism involves disinhibition; that is, inhibitory local circuit neurons are inhibited. The direct mechanism involves blockade of potassium conductances that slow neuronal discharge. Depending on the type of neuron, this effect is mediated by either α_1 or β receptors. Facilitation of excitatory synaptic transmission is in accordance with many of the behavioral processes thought to involve noradrenergic pathways, eg, attention and arousal.

C. 5-Hydroxytryptamine

Most 5-hydroxytryptamine (5-HT, serotonin) pathways originate from neurons in the raphe or midline regions of the pons and upper brainstem. 5-HT is contained in unmyelinated fibers that diffusely innervate most regions of the CNS, but the density of the innervation varies. 5-HT acts on more than a dozen receptor subtypes. Except for the 5-HT_3 receptor, all of these receptors are metabotropic. The ionotropic 5-HT_3 receptor exerts a rapid excitatory action at a very limited number of sites in the CNS. In most areas of the CNS, 5-HT has a strong inhibitory action. This action is mediated by 5-HT_{1A} receptors and is associated with membrane hyperpolarization caused by an increase in potassium conductance. It has been found that 5-HT_{1A} receptors and $GABA_B$ receptors activate the same population of potassium channels. Some cell types are slowly excited by 5-HT owing to its blockade of potassium channels via 5-HT_2 or 5-HT_4 receptors. Both excitatory and inhibitory actions can occur on the same neuron. It has often been speculated that 5-HT pathways may be involved in the hallucinations induced by LSD (lysergic acid), since this compound can antagonize the peripheral actions of 5-HT. However, LSD does not appear to be a 5-HT antagonist in the CNS, and typical LSD-induced behavior is still seen in animals after raphe nuclei are destroyed. Other proposed regulatory functions of 5-HT-containing neurons include sleep, temperature, appetite, and neuroendocrine control.

Peptides

A great many CNS peptides have been discovered that produce dramatic effects both on animal behavior and on the activity of individual neurons. Many of the peptides have been mapped with immunohistochemical techniques and include opioid peptides (eg, enkephalins, endorphins), neurotensin, substance P, somatostatin, cholecystokinin, vasoactive intestinal polypeptide, neuropeptide Y, and thyrotropin-releasing hormone. As in the peripheral autonomic nervous system, peptides often coexist with a conventional nonpeptide transmitter in the same neuron. A good example of the approaches used to define the role of these peptides in the CNS comes from studies on substance P and its association with sensory fibers. Substance P is contained in and released from small unmyelinated primary sensory neurons in the spinal cord and brainstem and causes a slow excitatory postsynaptic potential in target neurons. These sensory fibers are known to transmit noxious stimuli, and it is therefore surprising that—although substance P receptor antagonists can modify responses to certain types of pain—they do not block the response. Glutamate, which is released with substance P from these synapses, presumably plays an important role in transmitting pain stimuli. Substance P is certainly involved in many other functions because it is found in many areas of the CNS that are unrelated to pain pathways.

Many of these peptides are also found in peripheral structures, including peripheral synapses. They are described in Chapters 6 and 17.

Nitric Oxide

The CNS contains a substantial amount of nitric oxide synthase (NOS) within certain classes of neurons. This neuronal

NOS is an enzyme activated by calcium-calmodulin, and activation of NMDA receptors, which increases intracellular calcium, results in the generation of nitric oxide. Although a physiologic role for nitric oxide has been clearly established for vascular smooth muscle, its role in synaptic transmission and synaptic plasticity remains controversial. Perhaps the strongest case for a role of nitric oxide in neuronal signaling in the CNS is for long-term depression of synaptic transmission in the cerebellum.

Endocannabinoids

The primary psychoactive ingredient in cannabis, Δ^9-tetrahydrocannabinol (Δ^9-THC), affects the brain mainly by activating a specific cannabinoid receptor, CB_1. CB_1 receptors are expressed at high levels in many brain regions, and they are primarily located on presynaptic terminals. Several endogenous brain lipids, including anandamide and 2-arachidonylglycerol (2-AG), have been identified as CB_1 ligands. These ligands are not stored, as are classic neurotransmitters, but instead are rapidly synthesized by neurons in response to depolarization and consequent calcium influx. Activation of metabotropic receptors (eg, by acetylcholine and glutamate) can also activate the formation of 2-AG. In further contradistinction to classic neurotransmitters, endogenous cannabinoids can function as retrograde synaptic messengers: They are released from postsynaptic neurons and travel backward across synapses, activating CB_1 receptors on presynaptic neurons and suppressing transmitter release. This suppression can be transient or long lasting, depending on the pattern of activity. Cannabinoids may affect memory, cognition, and pain perception by this mechanism.

REFERENCES

Aizenman CD et al: Use-dependent changes in synaptic strength at the Purkinje cell to deep nuclear synapse. Prog Brain Res 2000;124:257.

Bredt DS, Nicoll RA: AMPA receptor trafficking at excitatory synapses. Neuron 2003;40:361.

Catterall WA et al: Compendium of voltage-gated ion channels: Calcium channels. Pharmacol Rev 2003;55:579.

Catterall WA, Goldin AL, Waxman SG: Compendium of voltage-gated ion channels: Sodium channels. Pharmacol Rev 2003;55:575.

Clapham DE et al: Compendium of voltage-gated ion channels: Transient receptor potential channels. Pharmacol Rev 2003;55:591.

Fremeau RT, Jr et al: VGLUTs define subsets of excitatory neurons and suggest novel roles for glutamate. Trends Neurosci 2004;27:98.

Freund TF, Katona I, Piomelli D: Role of endogenous cannabinoids in synaptic signaling. Physiol Rev 2003;83:1017.

Gouaux E, MacKinnon R: Principles of selective ion transport in channels and pumps. Science 2005;310:1461.

Hall ZW: In: *An Introduction to Molecular Neurobiology.* Sinauer, 1992.

Hille B: *Ionic Channels of Excitable Membranes*, 3rd ed. Sinauer, 2001.

Julius D, Basbaum AI: Molecular mechanisms of nociception. Nature 2001;413:203.

Koles L, Furst S, Illes P: P2X and P2Y receptors as possible targets of therapeutic manipulations in CNS illnesses. Drug News Perspect 2005;18:85.

Malenka RC, Nicoll RA: Long-term potentiation—A decade of progress? Science 1999;285:1870.

Mody I, Pearce RA: Diversity of inhibitory neurotransmission through GABA(A) receptors. Trends Neurosci 2004;27:569.

Moran MM, Xu H, Clapham DE: TRP ion channels in the nervous system. Curr Opin Neurobiol 2004;14:362.

Nestler EJ, Hyman SE, Malenka RC: *Molecular Neuropharmacology,* 2nd ed. McGraw-Hill, 2009.

Rudolph U, Mohler H: Analysis of GABAA receptor function and dissection of the pharmacology of benzodiazepines and general anesthetics through mouse genetics. Annu Rev Pharmacol Toxicol 2004;44:475.

Sudhof TC: The synaptic vesicle cycle. Annu Rev Neurosci 2004;27:509.

Wilson RI, Nicoll RA: Endocannabinoid signaling in the brain. Science 2002;296:678.

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CHAPTER 22

Sedative-Hypnotic Drugs

Anthony J. Trevor, PhD, & Walter L. Way, MD

CASE STUDY

At her annual physical examination, a 53-year-old middle school teacher complains that she has been experiencing difficulty falling asleep and after falling asleep awakens several times during the night. These episodes occur almost nightly and are having a negative impact on her teaching functions. She has tried various over-the-counter sleep remedies, but they were of little help and she experienced "hangover" effects the next day. Her general health is good, she is not overweight, and she takes no prescription drugs. She drinks one cup of decaffeinated coffee in the morning; however, she drinks as many as six cans per day of diet cola. She drinks a glass of wine with her evening meal but does not like stronger spirits. What other aspects of this patient's history would you like to know? What therapeutic measures are appropriate for this patient? What drug, or drugs (if any), would you prescribe?

Assignment of a drug to the sedative-hypnotic class indicates that it is able to cause sedation (with concomitant relief of anxiety) or to encourage sleep. Because there is considerable chemical variation within the group, this drug classification is based on clinical uses rather than on similarities in chemical structure. Anxiety states and sleep disorders are common problems, and sedative-hypnotics are widely prescribed drugs worldwide.

BASIC PHARMACOLOGY OF SEDATIVE-HYPNOTICS

An effective **sedative** (anxiolytic) agent should reduce anxiety and exert a calming effect. The degree of central nervous system depression caused by a sedative should be the minimum consistent with therapeutic efficacy. A **hypnotic** drug should produce drowsiness and encourage the onset and maintenance of a state of sleep. Hypnotic effects involve more pronounced depression of the central nervous system than sedation, and this can be achieved with many drugs in this class simply by increasing the dose. Graded dose-dependent depression of central nervous system function is a characteristic of most sedative-hypnotics. However, individual drugs differ in the relationship between the dose and the degree of central nervous system depression. Two examples of such dose-response relationships are shown in Figure 22–1. The linear slope for drug A is typical of many of the older sedative-hypnotics, including the barbiturates and alcohols. With such drugs, an increase in dose higher than that needed for hypnosis may lead to a state of general anesthesia. At still higher doses, these sedative-hypnotics may depress respiratory and vasomotor centers in the medulla, leading to coma and death. Deviations from a linear dose-response relationship, as shown for drug B, require proportionately greater dosage increments to achieve central nervous system depression more profound than hypnosis. This appears to be the case for benzodiazepines and for certain newer hypnotics that have a similar mechanism of action.

Chemical Classification

The **benzodiazepines** are widely used sedative-hypnotics. All of the structures shown in Figure 22–2 are 1,4-benzodiazepines, and most contain a carboxamide group in the 7-membered heterocyclic ring structure. An electronegative substituent in the 7 position, such as a halogen or a nitro group, is required for sedative-hypnotic activity. The structures of triazolam and alprazolam include the addition of a triazole ring at the 1,2-position.

The chemical structures of some older and less commonly used sedative-hypnotics, including several **barbiturates**, are shown in Figure 22–3. Glutethimide and meprobamate are of distinctive chemical structure but are practically equivalent to barbiturates in their pharmacologic effects. They are rarely used. The sedative-

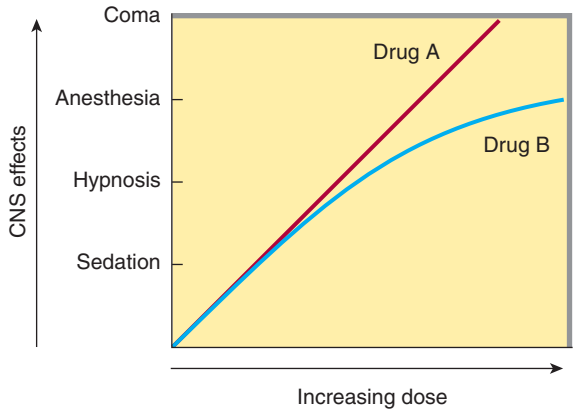

FIGURE 22–1 Dose-response curves for two hypothetical sedative-hypnotics.

hypnotic class also includes compounds of simpler chemical structure, including **ethanol** (see Chapter 23) and **chloral hydrate.**

Several drugs with novel chemical structures have been introduced more recently for use in sleep disorders. **Zolpidem**, an imidazopyridine, **zaleplon**, a pyrazolopyrimidine, and **eszopiclone**, a cyclopyrrolone (Figure 22–4), although structurally unrelated to benzodiazepines, share a similar mechanism of action, as described below. Eszopiclone is the *(S)*-enantiomer of zopiclone, a hypnotic drug that has been available outside the United States since 1989. **Ramelteon**, a melatonin receptor agonist, is a more recently introduced hypnotic drug (see Box: Ramelteon). **Buspirone** is a slow-onset anxiolytic agent whose actions are quite different from those of conventional sedative-hypnotics (see Box: Buspirone).

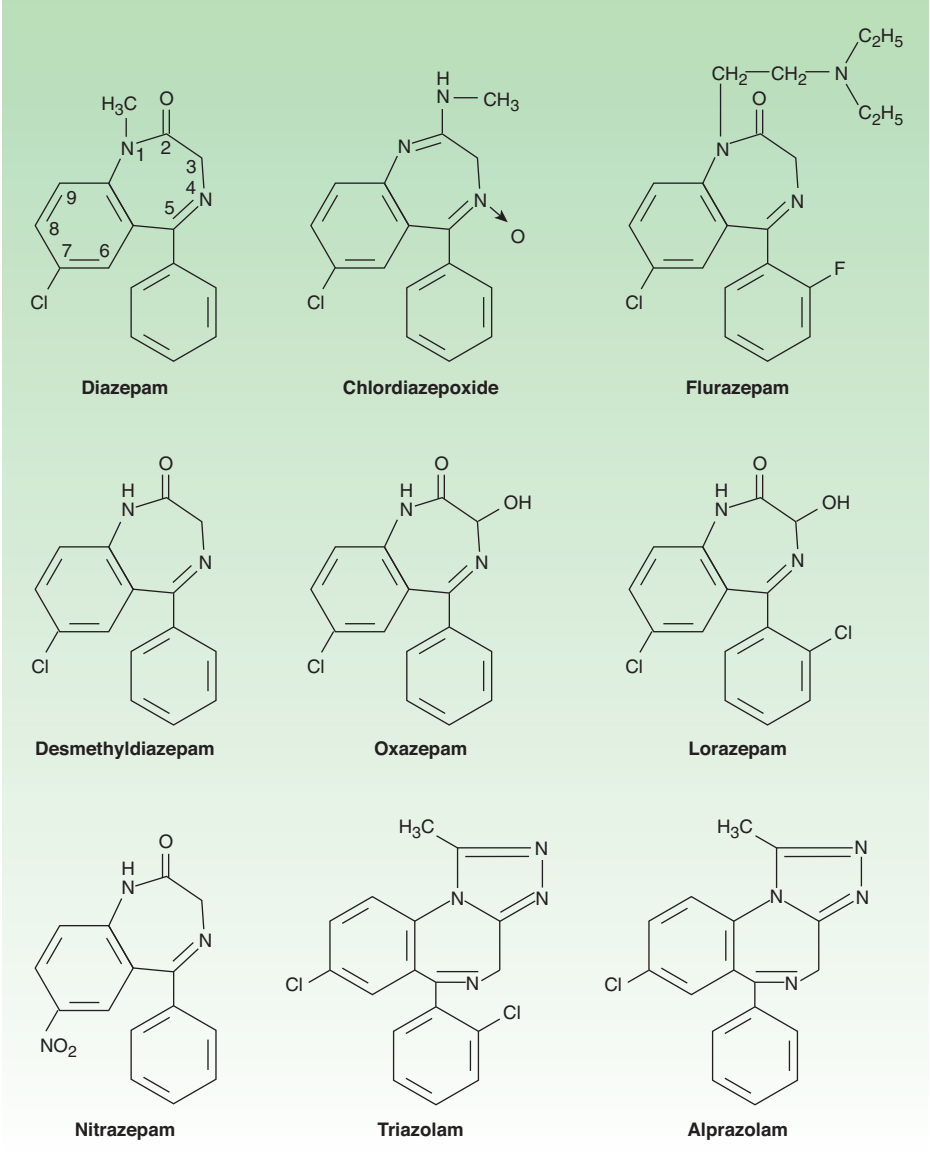

FIGURE 22–2 Chemical structures of some benzodiazepines.

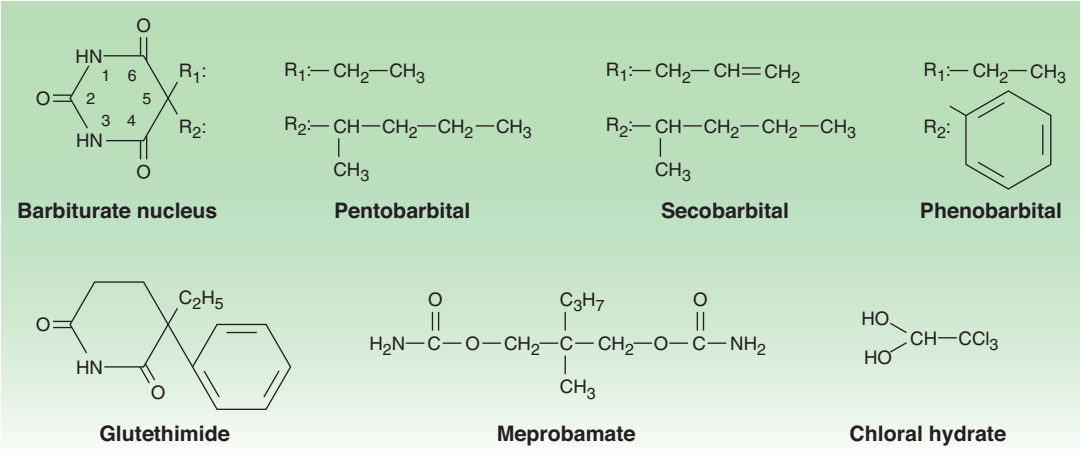

FIGURE 22–3 Chemical structures of some barbiturates and other sedative-hypnotics.

Other classes of drugs that exert sedative effects include antipsychotics (see Chapter 29) and many antidepressant drugs (see Chapter 30). The latter are currently used widely in the management of chronic anxiety disorders. Certain antihistaminic agents including diphenhydramine, hydroxyzine, and promethazine (see Chapter 16) cause sedation but commonly also exert marked effects on the peripheral autonomic nervous system. Antihistaminic drugs with sedative effects are available as over-the-counter sleep aids.

Pharmacokinetics

A. Absorption and Distribution

The rates of oral absorption of sedative-hypnotics differ depending on a number of factors, including lipophilicity. For example, the absorption of triazolam is extremely rapid, and that of diazepam and the active metabolite of clorazepate is more rapid than other commonly used benzodiazepines. Clorazepate, a prodrug, is converted to its active form, desmethyldiazepam (nordiazepam), by acid hydrolysis in the stomach. Most of the barbiturates and other older sedative-hypnotics, as well as the newer hypnotics (eszopiclone, zaleplon, zolpidem), are absorbed rapidly into the blood following oral administration.

Lipid solubility plays a major role in determining the rate at which a particular sedative-hypnotic enters the central nervous system. This property is responsible for the rapid onset of central nervous system effects of triazolam, thiopental (see Chapter 25), and the newer hypnotics eszopiclone, zaleplon, and zolpidem.

All sedative-hypnotics cross the placental barrier during pregnancy. If sedative-hypnotics are given during the predelivery period, they may contribute to the depression of neonatal vital functions. Sedative-hypnotics are also detectable in breast milk and may exert depressant effects in the nursing infant.

B. Biotransformation

Metabolic transformation to more water-soluble metabolites is necessary for clearance of sedative-hypnotics from the body. The microsomal drug-metabolizing enzyme systems of the liver are

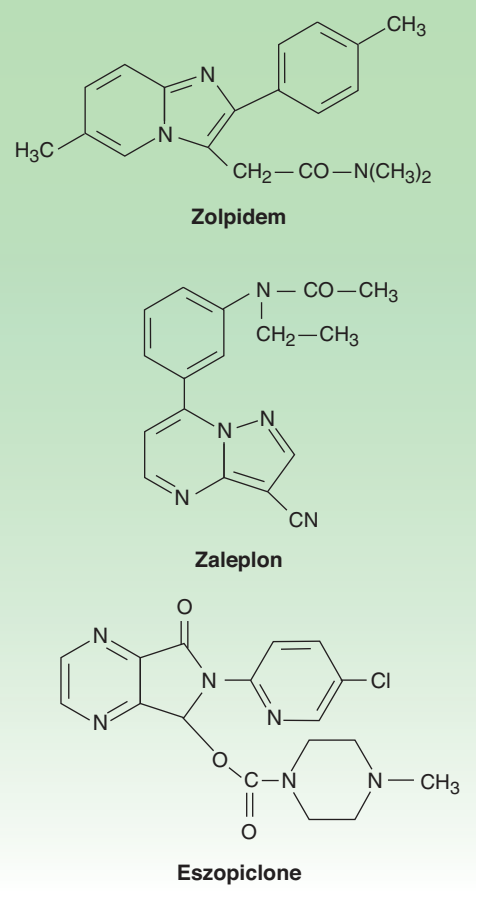

FIGURE 22–4 Chemical structures of newer hypnotics.

Ramelteon

Melatonin receptors are thought to be involved in maintaining circadian rhythms underlying the sleep-wake cycle (see Chapter 16). Ramelteon (Rozerem), a novel hypnotic drug specifically useful for patients who have difficulty in falling asleep, is an agonist at MT_1 and MT_2 melatonin receptors located in the suprachiasmatic nuclei of the brain. The drug has no direct effects on GABAergic neurotransmission in the central nervous system. In polysomnography studies of patients with chronic insomnia, ramelteon reduced the latency of persistent sleep with no effects on sleep architecture and no rebound insomnia or significant withdrawal symptoms. Ramelteon has minimal potential for abuse, is not a controlled substance, and regular use does not result in dependence. The drug is rapidly absorbed after oral administration and undergoes extensive first-pass metabolism, forming an active metabolite with longer half-life (2–5 hours) than the parent drug. The CYP1A2 isoform of cytochrome P450 is mainly responsible for the metabolism of ramelteon, but the CYP2C9 isoform is also involved. The drug should not be used in combination with inhibitors of CYP1A2 (eg, ciprofloxacin, fluvoxamine, tacrine, zileuton) or CYP2C9 (eg, fluconazole) and should be used with caution in patients with liver dysfunction. The CYP inducer rifampin markedly reduces the plasma levels of both ramelteon and its active metabolite. Adverse effects of ramelteon include dizziness, somnolence, fatigue, and endocrine changes as well as decreases in testosterone and increases in prolactin. Ramelteon is an FDA pregnancy category C drug.

Buspirone

Buspirone has selective anxiolytic effects, and its pharmacologic characteristics differ from those of other drugs described in this chapter. Buspirone relieves anxiety without causing marked sedative, hypnotic, or euphoric effects. Unlike benzodiazepines, the drug has no anticonvulsant or muscle relaxant properties. Buspirone does not interact directly with GABAergic systems. It may exert its anxiolytic effects by acting as a partial agonist at brain 5-HT_{1A} receptors, but it also has affinity for brain dopamine D_2 receptors. Buspirone-treated patients show no rebound anxiety or withdrawal signs on abrupt discontinuance. The drug is not effective in blocking the acute withdrawal syndrome resulting from abrupt cessation of use of benzodiazepines or other sedative-hypnotics. Buspirone has minimal abuse liability. In marked contrast to the benzodiazepines, the anxiolytic effects of buspirone may take more than a week to become established, making the drug unsuitable for management of acute anxiety states. The drug is used in generalized anxiety states but is less effective in panic disorders.

Buspirone is rapidly absorbed orally but undergoes extensive first-pass metabolism via hydroxylation and dealkylation reactions to form several active metabolites. The major metabolite is 1-(2-pyrimidyl)-piperazine (1-PP), which has α_2-adrenoceptor–blocking actions and which enters the central nervous system to reach higher levels than the parent drug. It is not known what role (if any) 1-PP plays in the central actions of buspirone. The elimination half-life of buspirone is 2–4 hours, and liver dysfunction may slow its clearance. Rifampin, an inducer of cytochrome P450, decreases the half-life of buspirone; inhibitors of CYP3A4 (eg, erythromycin, ketoconazole, grapefruit juice, nefazodone) can markedly increase its plasma levels.

Buspirone causes less psychomotor impairment than benzodiazepines and does not affect driving skills. The drug does not potentiate effects of conventional sedative-hypnotic drugs, ethanol, or tricyclic antidepressants, and elderly patients do not appear to be more sensitive to its actions. Nonspecific chest pain, tachycardia, palpitations, dizziness, nervousness, tinnitus, gastrointestinal distress, and paresthesias and a dose-dependent pupillary constriction may occur. Blood pressure may be significantly elevated in patients receiving MAO inhibitors. Buspirone is an FDA pregnancy category B drug.

most important in this regard, so elimination half-life of these drugs depends mainly on the rate of their metabolic transformation.

1. Benzodiazepines—Hepatic metabolism accounts for the clearance of all benzodiazepines. The patterns and rates of metabolism depend on the individual drugs. Most benzodiazepines undergo microsomal oxidation (phase I reactions), including *N*-dealkylation and aliphatic hydroxylation catalyzed by cytochrome P450 isozymes, especially CYP3A4. The metabolites are subsequently conjugated (phase II reactions) to form glucuronides that are excreted in the urine. However, many phase I metabolites of benzodiazepines are pharmacologically active, some with long half-lives (Figure 22–5). For example, desmethyldiazepam, which has an elimination half-life of more than 40 hours, is an active metabolite of chlordiazepoxide, diazepam, prazepam, and clorazepate. Alprazolam and triazolam undergo α-hydroxylation, and the resulting metabolites appear to exert short-lived pharmacologic effects because they are rapidly conjugated to form inactive glucuronides. The short elimination half-life of triazolam (2–3 hours) favors its use as a hypnotic rather than as a sedative drug.

The formation of active metabolites has complicated studies on the pharmacokinetics of the benzodiazepines in humans because the elimination half-life of the parent drug may have little relation to the time course of pharmacologic effects. Benzodiazepines for which the parent drug or active metabolites have long half-lives are predictably more likely to cause cumulative effects with multiple doses. Cumulative and residual effects such as excessive drowsiness appear to be less of a problem with such drugs as estazolam, oxazepam, and lorazepam, which have relatively short

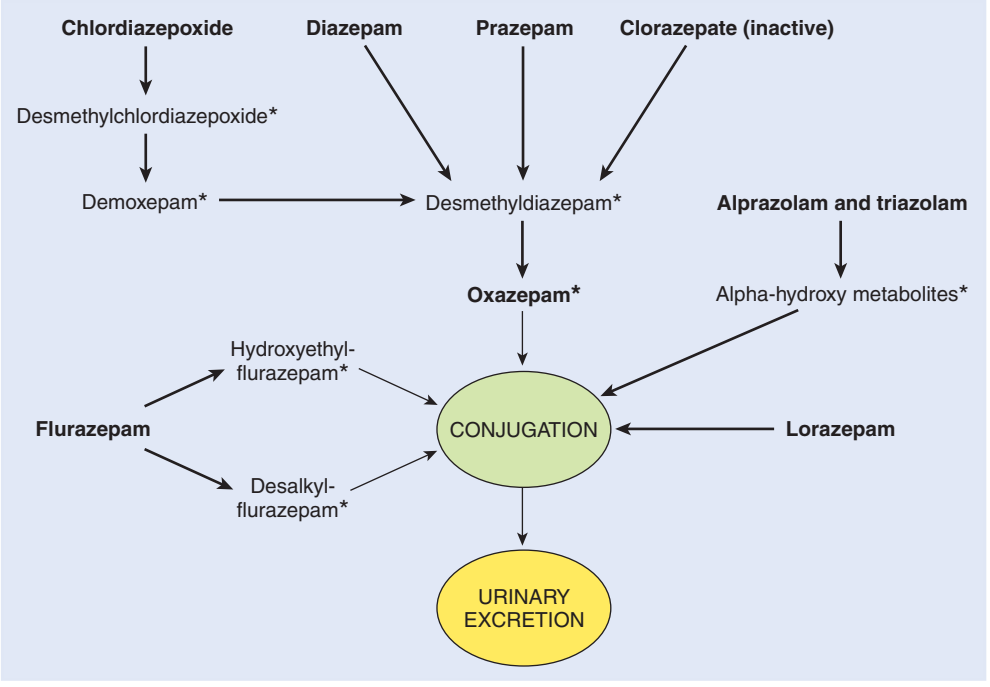

FIGURE 22–5 Biotransformation of benzodiazepines. (Boldface, drugs available for clinical use in various countries; *, active metabolite.)

half-lives and are metabolized directly to inactive glucuronides. Some pharmacokinetic properties of selected benzodiazepines are listed in Table 22–1. The metabolism of several commonly used benzodiazepines including diazepam, midazolam, and triazolam is affected by inhibitors and inducers of hepatic P450 isozymes (see Chapter 4).

2. Barbiturates—With the exception of phenobarbital, only insignificant quantities of the barbiturates are excreted unchanged. The major metabolic pathways involve oxidation by hepatic enzymes to form alcohols, acids, and ketones, which appear in the urine as glucuronide conjugates. The overall rate of hepatic metabolism in humans depends on the individual drug but (with the exception of the thiobarbiturates) is usually slow. The elimination half-lives of secobarbital and pentobarbital range from 18 to 48 hours in different individuals. The elimination half-life of phenobarbital in humans is 4–5 days. Multiple dosing with these agents can lead to cumulative effects.

3. Newer hypnotics—After oral administration of the standard formulation, zolpidem reaches peak plasma levels in 1.6 hours. A biphasic release formulation extends plasma levels by approximately

TABLE 22–1 Pharmacokinetic properties of some benzodiazepines and newer hypnotics in humans.

Drug	Peak Blood Level (hours)	Elimination Half-Life[1] (hours)	Comments
Alprazolam	1–2	12–15	Rapid oral absorption
Chlordiazepoxide	2–4	15–40	Active metabolites; erratic bioavailability from IM injection
Clorazepate	1–2 (nordiazepam)	50–100	Prodrug; hydrolyzed to active form in stomach
Diazepam	1–2	20–80	Active metabolites; erratic bioavailability from IM injection
Eszopiclone	1	6	Minor active metabolites
Flurazepam	1–2	40–100	Active metabolites with long half-lives
Lorazepam	1–6	10–20	No active metabolites
Oxazepam	2–4	10–20	No active metabolites
Temazepam	2–3	10–40	Slow oral absorption
Triazolam	1	2–3	Rapid onset; short duration of action
Zaleplon	< 1	1–2	Metabolized via aldehyde dehydrogenase
Zolpidem	1–3	1.5–3.5	No active metabolites

[1]Includes half-lives of major metabolites.

2 hours. Zolpidem is rapidly metabolized to inactive metabolites via oxidation and hydroxylation by hepatic cytochromes P450 including the CYP3A4 isozyme. The elimination half-life of the drug is 1.5–3.5 hours, with clearance decreased in elderly patients. Zaleplon is metabolized to inactive metabolites, mainly by hepatic aldehyde oxidase and partly by the cytochrome P450 isoform CYP3A4. The half-life of the drug is about 1 hour. Dosage should be reduced in patients with hepatic impairment and in the elderly. Cimetidine, which inhibits both aldehyde dehydrogenase and CYP3A4, markedly increases the peak plasma level of zaleplon. Eszopiclone is metabolized by hepatic cytochromes P450 (especially CYP3A4) to form the inactive *N*-oxide derivative and weakly active desmethyleszopiclone. The elimination half-life of eszopiclone is approximately 6 hours and is prolonged in the elderly and in the presence of inhibitors of CYP3A4 (eg, ketoconazole). Inducers of CYP3A4 (eg, rifampin) increase the hepatic metabolism of eszopiclone.

C. Excretion

The water-soluble metabolites of sedative-hypnotics, mostly formed via the conjugation of phase I metabolites, are excreted mainly via the kidney. In most cases, changes in renal function do not have a marked effect on the elimination of parent drugs. Phenobarbital is excreted unchanged in the urine to a certain extent (20–30% in humans), and its elimination rate can be increased significantly by alkalinization of the urine. This is partly due to increased ionization at alkaline pH, since phenobarbital is a weak acid with a pK_a of 7.4.

D. Factors Affecting Biodisposition

The biodisposition of sedative-hypnotics can be influenced by several factors, particularly alterations in hepatic function resulting from disease or drug-induced increases or decreases in microsomal enzyme activities (see Chapter 4).

In very old patients and in patients with severe liver disease, the elimination half-lives of these drugs are often increased significantly. In such cases, multiple normal doses of these sedative-hypnotics can result in excessive central nervous system effects.

The activity of hepatic microsomal drug-metabolizing enzymes may be increased in patients exposed to certain older sedative-hypnotics on a long-term basis (enzyme induction; see Chapter 4). Barbiturates (especially phenobarbital) and meprobamate are most likely to cause this effect, which may result in an increase in their own hepatic metabolism as well as that of other drugs. Increased biotransformation of other pharmacologic agents as a result of enzyme induction by barbiturates is a potential mechanism underlying drug interactions (see Chapter 66). In contrast, benzodiazepines and the newer hypnotics do not change hepatic drug-metabolizing enzyme activity with continuous use.

Pharmacodynamics of Benzodiazepines, Barbiturates, & Newer Hypnotics

A. Molecular Pharmacology of the $GABA_A$ Receptor

The benzodiazepines, the barbiturates, zolpidem, zaleplon, eszopiclone, and many other drugs bind to molecular components of the $GABA_A$ receptor in neuronal membranes in the central nervous system. This receptor, which functions as a chloride ion channel, is activated by the inhibitory neurotransmitter GABA (see Chapter 21).

The $GABA_A$ receptor has a pentameric structure assembled from five subunits (each with four membrane-spanning domains) selected from multiple polypeptide classes (α, β, γ, δ, ε, π, ρ, etc). Multiple subunits of several of these classes have been characterized, among them six different α (eg, α1 through α6), four β, and three γ. A model of the $GABA_A$ receptor-chloride ion channel macromolecular complex is shown in Figure 22–6.

A major isoform of the $GABA_A$ receptor that is found in many regions of the brain consists of two α1, two β2, and one γ2 subunits. In this isoform, the two binding sites for GABA are located between adjacent α1 and β2 subunits, and the binding pocket for benzodiazepines (the **BZ site** of the $GABA_A$ receptor) is between an α1 and the γ2 subunit. However, $GABA_A$ receptors in different areas of the central nervous system consist of various combinations of the essential subunits, and the benzodiazepines bind to many of these, including receptor isoforms containing α2, α3, and α5 subunits. Barbiturates also bind to multiple isoforms

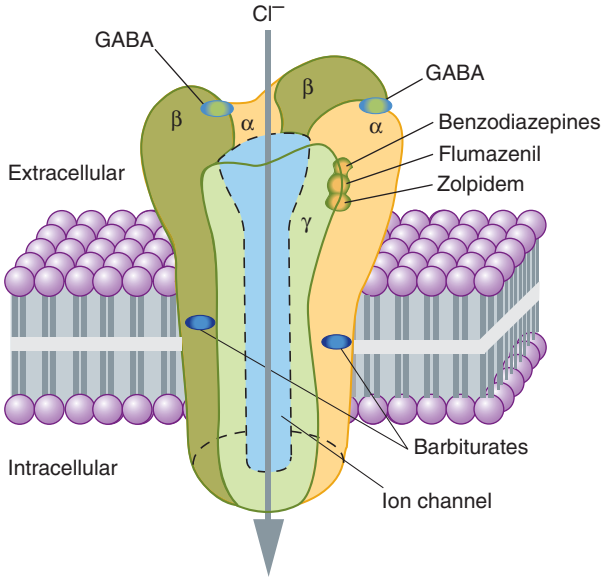

FIGURE 22–6 A model of the $GABA_A$ receptor-chloride ion channel macromolecular complex. A hetero-oligomeric glycoprotein, the complex consists of five or more membrane-spanning subunits. Multiple forms of α, β, and γ subunits are arranged in different pentameric combinations so that $GABA_A$ receptors exhibit molecular heterogeneity. GABA appears to interact at two sites between α and β subunits, triggering chloride channel opening with resulting membrane hyperpolarization. Binding of benzodiazepines and the newer hypnotic drugs such as zolpidem occurs at a single site between α and γ subunits, facilitating the process of chloride ion channel opening. The benzodiazepine antagonist flumazenil also binds at this site and can reverse the hypnotic effects of zolpidem. Note that these binding sites are distinct from those of the barbiturates. (See also text and Box: The Versatility of the Chloride Channel GABA Receptor Complex.)

of the $GABA_A$ receptor but at different sites from those with which benzodiazepines interact. In contrast to benzodiazepines, zolpidem, zaleplon, and eszopiclone bind more selectively because these drugs interact only with $GABA_A$-receptor isoforms that contain α1 subunits. The heterogeneity of $GABA_A$ receptors may constitute the molecular basis for the varied pharmacologic actions of benzodiazepines and related drugs (see Box: GABA Receptor Heterogeneity & Pharmacologic Selectivity).

In contrast to GABA itself, benzodiazepines and other sedative-hypnotics have a low affinity for $GABA_B$ receptors, which are activated by the spasmolytic drug baclofen (see Chapters 21 and 27).

B. Neuropharmacology

GABA (γ-aminobutyric acid) is a major inhibitory neurotransmitter in the central nervous system (see Chapter 21). Electrophysiologic studies have shown that benzodiazepines potentiate GABAergic inhibition at all levels of the neuraxis, including the spinal cord, hypothalamus, hippocampus, substantia nigra, cerebellar cortex, and cerebral cortex. Benzodiazepines appear to increase the efficiency of GABAergic synaptic inhibition. The benzodiazepines do not substitute for GABA but appear to enhance GABA's effects allosterically without directly activating $GABA_A$ receptors or opening the associated chloride channels. The enhancement in chloride ion conductance induced by the interaction of benzodiazepines with GABA takes the form of an increase in the *frequency* of channel-opening events.

Barbiturates also facilitate the actions of GABA at multiple sites in the central nervous system, but—in contrast to benzodiazepines—they appear to increase the *duration* of the GABA-gated chloride channel openings. At high concentrations, the barbiturates may also be GABA-mimetic, directly activating chloride channels. These effects involve a binding site or sites distinct from the benzodiazepine binding sites. Barbiturates are less selective in their actions than benzodiazepines, because they also depress the actions of the excitatory neurotransmitter glutamic acid via binding to the AMPA receptor. Barbiturates also exert nonsynaptic membrane effects in parallel with their effects on GABA and glutamate neurotransmission. This multiplicity of sites of action of barbiturates may be the basis for their ability to induce full surgical anesthesia (see Chapter 25) and for their more pronounced central depressant effects (which result in their low margin of safety) compared with benzodiazepines and the newer hypnotics.

C. Benzodiazepine Binding Site Ligands

The components of the $GABA_A$ receptor-chloride ion channel macromolecule that function as benzodiazepine binding sites exhibit heterogeneity (see Box: The Versatility of the Chloride Channel GABA Receptor Complex). Three types of ligand-benzodiazepine receptor interactions have been reported: (1) **Agonists** facilitate GABA actions, and this occurs at multiple BZ binding sites in the case of the benzodiazepines. As noted above, the nonbenzodiazepines zolpidem, zaleplon, and eszopiclone are selective agonists at the BZ sites that contain an α1 subunit. Endogenous agonist ligands for the BZ binding sites have been proposed, because benzodiazepine-like chemicals have been isolated from brain tissue of animals never exposed to these drugs. Nonbenzodiazepine molecules that have affinity for BZ sites on the $GABA_A$ receptor have also been detected in human brain. (2) **Antagonists** are typified by the synthetic benzodiazepine derivative **flumazenil,** which blocks the actions of benzodiazepines, eszopiclone, zaleplon, and zolpidem but does not antagonize the actions of barbiturates, meprobamate, or ethanol. Certain endogenous neuropeptides are also capable of blocking the interaction of benzodiazepines with BZ binding sites. (3) **Inverse agonists** act as negative allosteric modulators of GABA-receptor function (see Chapter 1). Their interaction with BZ sites on the $GABA_A$ receptor can *produce* anxiety and seizures, an action that has been demonstrated for several compounds, especially the β-carbolines, eg, *n*-butyl-β-carboline-3-carboxylate (β-CCB). In addition to their direct actions, these molecules can block the binding and the effects of benzodiazepines.

The physiologic significance of endogenous modulators of GABA functions in the central nervous system remains unclear. To date, it has not been established that the putative endogenous ligands of BZ binding sites play a role in the control of states of anxiety, sleep patterns, or any other characteristic behavioral expression of central nervous system function.

GABA Receptor Heterogeneity & Pharmacologic Selectivity

Studies involving strains of genetically engineered ("knockout") rodents have demonstrated that the specific pharmacologic actions elicited by benzodiazepines and other drugs that modulate GABA actions are influenced by the composition of the subunits assembled to form the $GABA_A$ receptor. Benzodiazepines interact primarily with brain $GABA_A$ receptors in which the α subunits (isoforms 1, 2, 3, and 5) have a conserved histidine residue in the N-terminal domain. Mice in which a point mutation has been inserted converting histidine to arginine in the α1 subunit show resistance to both the sedative and amnestic effects of benzodiazepines, but anxiolytic and muscle-relaxing effects are largely unchanged. These animals are also unresponsive to the hypnotic actions of zolpidem and zaleplon, drugs that bind selectively to $GABA_A$ receptors containing α1 subunits. In contrast, mice with selective histidine-arginine mutations in the α2 or α3 subunits of $GABA_A$ receptors show selective resistance to the antianxiety effects of benzodiazepines. Based on studies of this type, it has been suggested that α1 subunits in $GABA_A$ receptors mediate sedation, amnesia, and ataxic effects of benzodiazepines, whereas α2 and α3 subunits are involved in their anxiolytic and muscle-relaxing actions. Other mutation studies have led to suggestions that an α5 subtype is involved in at least some of the memory impairment caused by benzodiazepines. It should be emphasized that these studies involving genetic manipulations of the $GABA_A$ receptor utilize rodent models of the anxiolytic and amnestic actions of drugs.

The Versatility of the Chloride Channel GABA Receptor Complex

The $GABA_A$-chloride channel macromolecular complex is one of the most versatile drug-responsive machines in the body. In addition to the benzodiazepines, barbiturates, and the newer hypnotics (eg, zolpidem), many other drugs with central nervous system effects can modify the function of this important ionotropic receptor. These include alcohol and certain intravenous anesthetics (etomidate, propofol) in addition to thiopental. For example, etomidate and propofol (see Chapter 25) appear to act selectively at $GABA_A$ receptors that contain β2 and β3 subunits, the latter suggested to be the most important with respect to the hypnotic and muscle-relaxing actions of these anesthetic agents. The anesthetic steroid alphaxalone is thought to interact with $GABA_A$ receptors, and these receptors may also be targets for some of the actions of volatile anesthetics (eg, halothane). Most of these agents facilitate or mimic the action of GABA. However, it has not been shown that all these drugs act exclusively by this mechanism. Other drugs used in the management of seizure disorders indirectly influence the activity of the $GABA_A$-chloride channel macromolecular complex by inhibiting GABA metabolism (eg, vigabatrin) or reuptake of the transmitter (eg, tiagabine). Central nervous system excitatory agents that act on the chloride channel include picrotoxin and bicuculline. These convulsant drugs block the channel directly (picrotoxin) or interfere with GABA binding (bicuculline).

D. Organ Level Effects

1. Sedation—Benzodiazepines, barbiturates, and most older sedative-hypnotic drugs exert calming effects with concomitant reduction of anxiety at relatively low doses. In most cases, however, the anxiolytic actions of sedative-hypnotics are accompanied by some depressant effects on psychomotor and cognitive functions. In experimental animal models, benzodiazepines and older sedative-hypnotic drugs are able to disinhibit punishment-suppressed behavior. This disinhibition has been equated with antianxiety effects of sedative-hypnotics, and it is not a characteristic of all drugs that have sedative effects, eg, the tricyclic antidepressants and antihistamines. However, the disinhibition of previously suppressed behavior may be more related to behavioral disinhibitory effects of sedative-hypnotics, including euphoria, impaired judgment, and loss of self-control, which can occur at dosages in the range of those used for management of anxiety. The benzodiazepines also exert dose-dependent anterograde amnesic effects (inability to remember events occurring during the drug's duration of action).

2. Hypnosis—By definition, all of the sedative-hypnotics induce sleep if high enough doses are given. The effects of sedative-hypnotics on the stages of sleep depend on several factors, including the specific drug, the dose, and the frequency of its administration. The general effects of benzodiazepines and older sedative-hypnotics on patterns of normal sleep are as follows: (1) the latency of sleep onset is decreased (time to fall asleep); (2) the duration of stage 2 NREM (nonrapid eye movement) sleep is increased; (3) the duration of REM sleep is decreased; and (4) the duration of stage 4 NREM slow-wave sleep is decreased. The newer hypnotics all decrease the latency to persistent sleep. Zolpidem decreases REM sleep but has minimal effect on slow-wave sleep. Zaleplon decreases the latency of sleep onset with little effect on total sleep time, NREM, or REM sleep. Eszopiclone increases total sleep time, mainly via increases in stage 2 NREM sleep, and at low doses has little effect on sleep patterns. At the highest recommended dose, eszopiclone decreases REM sleep.

More rapid onset of sleep and prolongation of stage 2 are presumably clinically useful effects. However, the significance of sedative-hypnotic drug effects on REM and slow-wave sleep is not clear. Deliberate interruption of REM sleep causes anxiety and irritability followed by a rebound increase in REM sleep at the end of the experiment. A similar pattern of "REM rebound" can be detected following abrupt cessation of drug treatment with older sedative-hypnotics, especially when drugs with short durations of action (eg, triazolam) are used at high doses. With respect to zolpidem and the other newer hypnotics, there is little evidence of REM rebound when these drugs are discontinued after use of recommended doses. However, rebound insomnia occurs with both zolpidem and zaleplon if used at higher doses. Despite possible reductions in slow-wave sleep, there are no reports of disturbances in the secretion of pituitary or adrenal hormones when either barbiturates or benzodiazepines are used as hypnotics. The use of sedative-hypnotics for more than 1–2 weeks leads to some tolerance to their effects on sleep patterns.

3. Anesthesia—As shown in Figure 22–1, high doses of certain sedative-hypnotics depress the central nervous system to the point known as stage III of general anesthesia (see Chapter 25). However, the suitability of a particular agent as an adjunct in anesthesia depends mainly on the physicochemical properties that determine its rapidity of onset and duration of effect. Among the barbiturates, thiopental and methohexital are very lipid-soluble, penetrating brain tissue rapidly following intravenous administration, a characteristic favoring their use for the induction of anesthesia. Rapid tissue redistribution (not rapid elimination) accounts for the short duration of action of these drugs, a feature useful in recovery from anesthesia.

Benzodiazepines—including diazepam, lorazepam, and midazolam—are used intravenously in anesthesia (see Chapter 25), often in combination with other agents. Not surprisingly, benzodiazepines given in large doses as adjuncts to general anesthetics may contribute to a persistent postanesthetic respiratory depression. This is probably related to their relatively long half-lives and the formation of active metabolites. However, if necessary, such depressant actions of the benzodiazepines are usually reversible with flumazenil.

4. Anticonvulsant effects—Many sedative-hypnotics are capable of inhibiting the development and spread of epileptiform electrical activity in the central nervous system. Some selectivity exists in that some members of the group can exert anticonvulsant effects without marked central nervous system depression (although psychomotor function may be impaired). Several benzodiazepines—including clonazepam, nitrazepam, lorazepam, and diazepam—are sufficiently selective to be clinically useful in the management of seizures (see Chapter 24). Of the barbiturates, phenobarbital and metharbital (converted to phenobarbital in the body) are effective in the treatment of generalized tonic-clonic seizures, though not the drugs of first choice. Zolpidem, zaleplon, and eszopiclone lack anticonvulsant activity, presumably because of their more selective binding than that of benzodiazepines to $GABA_A$ receptor isoforms.

5. Muscle relaxation—Some sedative-hypnotics, particularly members of the carbamate (eg, meprobamate) and benzodiazepine groups, exert inhibitory effects on polysynaptic reflexes and internuncial transmission and at high doses may also depress transmission at the skeletal neuromuscular junction. Somewhat selective actions of this type that lead to muscle relaxation can be readily demonstrated in animals and have led to claims of usefulness for relaxing contracted voluntary muscle in muscle spasm (see Clinical Pharmacology). Muscle relaxation is not a characteristic action of zolpidem, zaleplon, and eszopiclone.

6. Effects on respiration and cardiovascular function—At hypnotic doses in healthy patients, the effects of sedative-hypnotics on respiration are comparable to changes during natural sleep. However, even at therapeutic doses, sedative-hypnotics can produce significant respiratory depression in patients with pulmonary disease. Effects on respiration are dose-related, and depression of the medullary respiratory center is the usual cause of death due to overdose of sedative-hypnotics.

At doses up to those causing hypnosis, no significant effects on the cardiovascular system are observed in healthy patients. However, in hypovolemic states, heart failure, and other diseases that impair cardiovascular function, normal doses of sedative-hypnotics may cause cardiovascular depression, probably as a result of actions on the medullary vasomotor centers. At toxic doses, myocardial contractility and vascular tone may both be depressed by central and peripheral effects, leading to circulatory collapse. Respiratory and cardiovascular effects are more marked when sedative-hypnotics are given intravenously.

Tolerance & Dependence

Tolerance—decreased responsiveness to a drug following repeated exposure—is a common feature of sedative-hypnotic use. It may result in the need for an increase in the dose required to maintain symptomatic improvement or to promote sleep. It is important to recognize that partial cross-tolerance occurs between the sedative-hypnotics described here and also with ethanol (see Chapter 23)—a feature of some clinical importance, as explained below. The mechanisms responsible for tolerance to sedative-hypnotics are not well understood. An increase in the rate of drug metabolism (metabolic tolerance) may be partly responsible in the case of chronic administration of barbiturates, but changes in responsiveness of the central nervous system (pharmacodynamic tolerance) are of greater importance for most sedative-hypnotics. In the case of benzodiazepines, the development of tolerance in animals has been associated with down-regulation of brain benzodiazepine receptors. Tolerance has been reported to occur with the extended use of zolpidem. Minimal tolerance was observed with the use of zaleplon over a 5-week period and eszopiclone over a 6-month period.

The perceived desirable properties of relief of anxiety, euphoria, disinhibition, and promotion of sleep have led to the compulsive misuse of virtually all sedative-hypnotics. (See Chapter 32 for a detailed discussion.) For this reason, most sedative-hypnotic drugs are classified as Schedule III or Schedule IV drugs for prescribing purposes in the United States. The consequences of abuse of these agents can be defined in both psychological and physiologic terms. The psychological component may initially parallel simple neurotic behavior patterns difficult to differentiate from those of the inveterate coffee drinker or cigarette smoker. When the pattern of sedative-hypnotic use becomes compulsive (addiction, see Chapter 32), more serious complications develop, including dependence and tolerance.

Dependence can be described as an altered physiologic state that requires continuous drug administration to prevent an abstinence or withdrawal syndrome. In the case of sedative-hypnotics, this syndrome is characterized by states of increased anxiety, insomnia, and central nervous system excitability that may progress to convulsions. Most sedative-hypnotics—including benzodiazepines—are capable of causing dependence when used on a long-term basis. However, the severity of withdrawal symptoms differs among individual drugs and depends also on the magnitude of the dose used immediately before cessation of use. When higher doses of sedative-hypnotics are used, abrupt withdrawal leads to more serious withdrawal signs. Differences in the severity of withdrawal symptoms resulting from individual sedative-hypnotics relate in part to half-life, since drugs with long half-lives are eliminated slowly enough to accomplish gradual withdrawal with few physical symptoms. The use of drugs with very short half-lives for hypnotic effects may lead to signs of withdrawal even between doses. For example, triazolam, a benzodiazepine with a half-life of about 4 hours, has been reported to cause daytime anxiety when used to treat sleep disorders. The abrupt cessation of use of zolpidem, zaleplon, or eszopiclone may also result in withdrawal symptoms, though usually of less intensity than those seen with benzodiazepines.

BENZODIAZEPINE ANTAGONISTS: FLUMAZENIL

Flumazenil is one of several 1,4-benzodiazepine derivatives with a high affinity for the benzodiazepine binding site on the $GABA_A$ receptor that act as competitive antagonists. It blocks many of the actions of benzodiazepines, zolpidem, zaleplon, and eszopiclone, but does not antagonize the central nervous system effects of other

sedative-hypnotics, ethanol, opioids, or general anesthetics. Flumazenil is approved for use in reversing the central nervous system depressant effects of benzodiazepine overdose and to hasten recovery following use of these drugs in anesthetic and diagnostic procedures. Although the drug reverses the sedative effects of benzodiazepines, antagonism of benzodiazepine-induced respiratory depression is less predictable. When given intravenously, flumazenil acts rapidly but has a short half-life (0.7–1.3 hours) due to rapid hepatic clearance. Because all benzodiazepines have a longer duration of action than flumazenil, sedation commonly recurs, requiring repeated administration of the antagonist.

Adverse effects of flumazenil include agitation, confusion, dizziness, and nausea. Flumazenil may cause a severe precipitated abstinence syndrome in patients who have developed marked benzodiazepine dependence. In patients who have ingested benzodiazepines with tricyclic antidepressants, seizures and cardiac arrhythmias may follow flumazenil administration.

■ CLINICAL PHARMACOLOGY OF SEDATIVE-HYPNOTICS

TREATMENT OF ANXIETY STATES

The psychological, behavioral, and physiological responses that characterize anxiety can take many forms. Typically, the psychic awareness of anxiety is accompanied by enhanced vigilance, motor tension, and autonomic hyperactivity. Anxiety is often secondary to organic disease states—acute myocardial infarction, angina pectoris, gastrointestinal ulcers, etc—which themselves require specific therapy. Another class of secondary anxiety states (situational anxiety) results from circumstances that may have to be dealt with only once or a few times, including anticipation of frightening medical or dental procedures and family illness or other stressful event. Even though situational anxiety tends to be self-limiting, the short-term use of sedative-hypnotics may be appropriate for the treatment of this and certain disease-associated anxiety states. Similarly, the use of a sedative-hypnotic as premedication prior to surgery or some unpleasant medical procedure is rational and proper (Table 22–2).

TABLE 22–2 Clinical uses of sedative-hypnotics.

For relief of anxiety
For insomnia
For sedation and amnesia before and during medical and surgical procedures
For treatment of epilepsy and seizure states
As a component of balanced anesthesia (intravenous administration)
For control of ethanol or other sedative-hypnotic withdrawal states
For muscle relaxation in specific neuromuscular disorders
As diagnostic aids or for treatment in psychiatry

Excessive or unreasonable anxiety about life circumstances (generalized anxiety disorder, GAD), panic disorders, and agoraphobia are also amenable to drug therapy, sometimes in conjunction with psychotherapy. The benzodiazepines continue to be used for the management of acute anxiety states and for rapid control of panic attacks. They are also used, though much less commonly than in the past, in the long-term management of GAD and panic disorders. Anxiety symptoms may be relieved by many benzodiazepines, but it is not always easy to demonstrate the superiority of one drug over another. Alprazolam has been used in the treatment of panic disorders and agoraphobia and appears to be more selective in these conditions than other benzodiazepines. The choice of benzodiazepines for the treatment of anxiety is based on several sound pharmacologic principles: (1) a rapid onset of action; (2) a relatively high therapeutic index (see drug B in Figure 22–1), plus availability of flumazenil for treatment of overdose; (3) a low risk of drug interactions based on liver enzyme induction; and (4) minimal effects on cardiovascular or autonomic functions.

Disadvantages of the benzodiazepines include the risk of dependence, depression of central nervous system functions, and amnestic effects. In addition, the benzodiazepines exert additive central nervous system depression when administered with other drugs, including ethanol. The patient should be warned of this possibility to avoid impairment of performance of any task requiring mental alertness and motor coordination. In the treatment of generalized anxiety disorders and certain phobias, newer antidepressants, including selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), are now considered by many authorities to be drugs of first choice (see Chapter 30). However, these agents have a slow onset of action and thus, limited effectiveness in acute anxiety states.

Sedative-hypnotics should be used with appropriate caution so as to minimize adverse effects. A dose should be prescribed that does not impair mentation or motor functions during waking hours. Some patients may tolerate the drug better if most of the daily dose is given at bedtime, with smaller doses during the day. Prescriptions should be written for short periods, since there is little justification for long-term therapy (defined as use of therapeutic doses for 2 months or longer). The physician should make an effort to assess the efficacy of therapy from the patient's subjective responses. Combinations of antianxiety agents should be avoided, and people taking sedatives should be cautioned about the consumption of alcohol and the concurrent use of over-the-counter medications containing antihistaminic or anticholinergic drugs (see Chapter 63).

TREATMENT OF SLEEP PROBLEMS

Sleep disorders are common and often result from inadequate treatment of underlying medical conditions or psychiatric illness. True primary insomnia is rare. Nonpharmacologic therapies that are useful for sleep problems include proper diet and exercise, avoiding stimulants before retiring, ensuring a comfortable sleeping environment, and retiring at a regular time each night. In some cases, however, the patient will need and should be given a sedative-hypnotic for a

limited period. It should be noted that the abrupt discontinuance of many drugs in this class can lead to rebound insomnia.

Benzodiazepines can cause a dose-dependent decrease in both REM and slow-wave sleep, though to a lesser extent than the barbiturates. The newer hypnotics zolpidem, zaleplon, and eszopiclone are less likely than the benzodiazepines to change sleep patterns. However, so little is known about the clinical impact of these effects that statements about the desirability of a particular drug based on its effects on sleep architecture have more theoretical than practical significance. Clinical criteria of efficacy in alleviating a particular sleeping problem are more useful. The drug selected should be one that provides sleep of fairly rapid onset (decreased sleep latency) and sufficient duration, with minimal "hangover" effects such as drowsiness, dysphoria, and mental or motor depression the following day. Older drugs such as chloral hydrate, secobarbital, and pentobarbital continue to be used occasionally, but zolpidem, zaleplon, eszopiclone, or benzodiazepines are generally preferred. Daytime sedation is more common with benzodiazepines that have slow elimination rates (eg, lorazepam) and those that are biotransformed to active metabolites (eg, flurazepam, quazepam). If benzodiazepines are used nightly, tolerance can occur, which may lead to dose increases by the patient to produce the desired effect. Anterograde amnesia occurs to some degree with all benzodiazepines used for hypnosis.

Eszopiclone, zaleplon, and zolpidem have efficacies similar to those of the hypnotic benzodiazepines in the management of sleep disorders. Favorable clinical features of zolpidem and the other newer hypnotics include rapid onset of activity and modest day-after psychomotor depression with few amnestic effects. Zolpidem, one of the most frequently prescribed hypnotic drugs in the United States, is available in a biphasic release formulation that provides sustained drug levels for sleep maintenance. Zaleplon acts rapidly, and because of its short half-life, the drug has value in the management of patients who awaken early in the sleep cycle. At recommended doses, zaleplon and eszopiclone (despite its relatively long half-life) appear to cause less amnesia or day-after somnolence than zolpidem or benzodiazepines. The drugs in this class commonly used for sedation and hypnosis are listed in Table 22–3 together with recommended doses.

Note: The failure of insomnia to remit after 7–10 days of treatment may indicate the presence of a primary psychiatric or medical illness that should be evaluated. Long-term use of hypnotics is an irrational and dangerous medical practice.

OTHER THERAPEUTIC USES

Table 22–2 summarizes several other important clinical uses of drugs in the sedative-hypnotic class. Drugs used in the management of seizure disorders and as intravenous agents in anesthesia are discussed in Chapters 24 and 25.

For sedative and possible amnestic effects during medical or surgical procedures such as endoscopy and bronchoscopy—as well as for premedication prior to anesthesia—oral formulations of shorter-acting drugs are preferred.

Long-acting drugs such as chlordiazepoxide and diazepam and, to a lesser extent, phenobarbital are administered in progressively decreasing doses to patients during withdrawal from physiologic dependence on ethanol or other sedative-hypnotics. Parenteral lorazepam is used to suppress the symptoms of delirium tremens.

Meprobamate and the benzodiazepines have frequently been used as central muscle relaxants, though evidence for general efficacy without accompanying sedation is lacking. A possible exception is diazepam, which has useful relaxant effects in skeletal muscle spasticity of central origin (see Chapter 27).

Psychiatric uses of benzodiazepines other than treatment of anxiety states include the initial management of mania and the control of drug-induced hyperexcitability states (eg, phencyclidine intoxication). Sedative-hypnotics are also used occasionally as diagnostic aids in neurology and psychiatry.

TABLE 22–3 Dosages of drugs used commonly for sedation and hypnosis.

Sedation		Hypnosis	
Drug	**Dosage**	**Drug**	**Dosage (at Bedtime)**
Alprazolam	0.25–0.5 mg 2–3 times daily	Chloral hydrate	500–1000 mg
Buspirone	5–10 mg 2–3 times daily	Estazolam	0.5–2 mg
Chlordiazepoxide	10–20 mg 2–3 times daily	Eszopiclone	1–3 mg
Clorazepate	5–7.5 mg twice daily	Lorazepam	2–4 mg
Diazepam	5 mg twice daily	Quazepam	7.5–15 mg
Halazepam	20–40 mg 3–4 times daily	Secobarbital	100–200 mg
Lorazepam	1–2 mg once or twice daily	Temazepam	7.5–30 mg
Oxazepam	15–30 mg 3–4 times daily	Triazolam	0.125–0.5 mg
Phenobarbital	15–30 mg 2–3 times daily	Zaleplon	5–20 mg
		Zolpidem	5–10 mg

CLINICAL TOXICOLOGY OF SEDATIVE-HYPNOTICS

Direct Toxic Actions

Many of the common adverse effects of sedative-hypnotics result from dose-related depression of the central nervous system. Relatively low doses may lead to drowsiness, impaired judgment, and diminished motor skills, sometimes with a significant impact on driving ability, job performance, and personal relationships. Sleep driving and other somnambulistic behavior with no memory of the event has occurred with the sedative-hypnotic drugs used in sleep disorders, prompting the Food and Drug Administration in 2007 to issue warnings of this potential hazard. Benzodiazepines may cause a significant dose-related anterograde amnesia; they can significantly impair ability to learn new information, particularly that involving effortful cognitive processes, while leaving the retrieval of previously learned information intact. This effect is utilized for uncomfortable clinical procedures, eg, endoscopy, because the patient is able to cooperate during the procedure but amnesic regarding it afterward. The criminal use of benzodiazepines in cases of "date rape" is based on their dose-dependent amnestic effects. Hangover effects are not uncommon following use of hypnotic drugs with long elimination half-lives. Because elderly patients are more sensitive to the effects of sedative-hypnotics, doses approximately half of those used in younger adults are safer and usually as effective. *The most common reversible cause of confusional states in the elderly is overuse of sedative-hypnotics.* At higher doses, toxicity may present as lethargy or a state of exhaustion or, alternatively, as gross symptoms equivalent to those of ethanol intoxication. The physician should be aware of variability among patients in terms of doses causing adverse effects. An increased sensitivity to sedative-hypnotics is more common in patients with cardiovascular disease, respiratory disease, or hepatic impairment and in older patients. Sedative-hypnotics can exacerbate breathing problems in patients with chronic pulmonary disease and in those with symptomatic sleep apnea.

Sedative-hypnotics are the drugs most frequently involved in deliberate overdoses, in part because of their general availability as very commonly prescribed pharmacologic agents. The benzodiazepines are considered to be safer drugs in this respect, since they have flatter dose-response curves. Epidemiologic studies on the incidence of drug-related deaths support this general assumption—eg, 0.3 deaths per million tablets of diazepam prescribed versus 11.6 deaths per million capsules of secobarbital in one study. Alprazolam is purportedly more toxic in overdose than other benzodiazepines. Of course, many factors other than the specific sedative-hypnotic could influence such data—particularly the presence of other central nervous system depressants, including ethanol. In fact, most serious cases of drug overdosage, intentional or accidental, do involve polypharmacy; and when combinations of agents are taken, the practical safety of benzodiazepines may be less than the foregoing would imply.

The lethal dose of any sedative-hypnotic varies with the patient and the circumstances (see Chapter 58). If discovery of the ingestion is made early and a conservative treatment regimen is started, the outcome is rarely fatal, even following very high doses. On the other hand, for most sedative-hypnotics—with the exception of benzodiazepines and possibly the newer hypnotic drugs that have a similar mechanism of action—a dose as low as ten times the hypnotic dose may be fatal if the patient is not discovered or does not seek help in time. With severe toxicity, the respiratory depression from central actions of the drug may be complicated by aspiration of gastric contents in the unattended patient—an even more likely occurrence if ethanol is present. Cardiovascular depression further complicates successful resuscitation. In such patients, treatment consists of ensuring a patent airway, with mechanical ventilation if needed, and maintenance of plasma volume, renal output, and cardiac function. Use of a positive inotropic drug such as dopamine, which preserves renal blood flow, is sometimes indicated. Hemodialysis or hemoperfusion may be used to hasten elimination of some of these drugs.

Flumazenil reverses the sedative actions of benzodiazepines, and those of eszopiclone, zaleplon, and zolpidem, although experience with its use in overdose of the newer hypnotics is limited. However, its duration of action is short, its antagonism of respiratory depression is unpredictable, and there is a risk of precipitation of withdrawal symptoms in long-term users of benzodiazepines (see below). Consequently, the use of flumazenil in benzodiazepine overdose *must* be accompanied by adequate monitoring and support of respiratory function. The extensive clinical use of triazolam has led to reports of serious central nervous system effects including behavioral disinhibition, delirium, aggression, and violence. Although behavioral disinhibition may occur with any sedative-hypnotic drug, it does not appear to be more prevalent with triazolam than with other benzodiazepines. Disinhibitory reactions during benzodiazepine treatment are more clearly associated with the use of very high doses and the pretreatment level of patient hostility.

Adverse effects of the sedative-hypnotics that are not referable to their central nervous system actions occur infrequently. Hypersensitivity reactions, including skin rashes, occur only occasionally with most drugs of this class. Reports of teratogenicity leading to fetal deformation following use of certain benzodiazepines have resulted in FDA assignment of individual benzodiazepines to either category D or X in terms of pregnancy risk. Most barbiturates are FDA pregnancy category D. Eszopiclone, ramelteon, zaleplon, and zolpidem are category C, while buspirone is a pregnancy category B drug. Because barbiturates enhance porphyrin synthesis, they are *absolutely contraindicated* in patients with a history of acute intermittent porphyria, variegate porphyria, hereditary coproporphyria, or symptomatic porphyria.

Alterations in Drug Response

Depending on the dosage and the duration of use, tolerance occurs in varying degrees to many of the pharmacologic effects of sedative-hypnotics. However, it should not be assumed that the degree of tolerance achieved is identical for all pharmacologic effects. There is evidence that the lethal dose range is not altered

significantly by the long-term use of sedative-hypnotics. Cross-tolerance between the different sedative-hypnotics, including ethanol, can lead to an unsatisfactory therapeutic response when standard doses of a drug are used in a patient with a recent history of excessive use of these agents. However, there have been very few reports of tolerance development when eszopiclone, zolpidem, or zaleplon was used for less than 4 weeks.

With the long-term use of sedative-hypnotics, especially if doses are increased, a state of dependence can occur. This may develop to a degree unparalleled by any other drug group, *including the opioids.* Withdrawal from a sedative-hypnotic can have severe and life-threatening manifestations. Withdrawal symptoms range from restlessness, anxiety, weakness, and orthostatic hypotension to hyperactive reflexes and generalized seizures. Symptoms of withdrawal are usually more severe following discontinuance of sedative-hypnotics with shorter half-lives. However, eszopiclone, zolpidem, and zaleplon appear to be exceptions to this, because withdrawal symptoms are minimal following abrupt discontinuance of these newer short-acting agents. Symptoms are less pronounced with longer-acting drugs, which may partly accomplish their own tapered withdrawal by virtue of their slow elimination. Cross-dependence, defined as the ability of one drug to suppress abstinence symptoms from discontinuance of another drug, is quite marked among sedative-hypnotics. This provides the rationale for therapeutic regimens in the management of withdrawal states: Longer-acting drugs such as chlordiazepoxide, diazepam, and phenobarbital can be used to alleviate withdrawal symptoms of shorter-acting drugs, including ethanol.

Drug Interactions

The most common drug interactions involving sedative-hypnotics are interactions with other central nervous system depressant drugs, leading to additive effects. These interactions have some therapeutic usefulness when these drugs are used as adjuvants in anesthesia practice. However, if not anticipated, such interactions can lead to serious consequences, including enhanced depression with concomitant use of many other drugs. Additive effects can be predicted with concomitant use of alcoholic beverages, opioid analgesics, anticonvulsants, and phenothiazines. Less obvious but just as important is enhanced central nervous system depression with a variety of antihistamines, antihypertensive agents, and antidepressant drugs of the tricyclic class.

Interactions involving changes in the activity of hepatic drug-metabolizing enzyme systems have been discussed (see also Chapters 4 and 66).

SUMMARY Sedative-Hypnotics

Subclass and Examples	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
BENZODIAZEPINES				
• Alprazolam • Chlordiazepoxide • Clorazepate • Clonazepam • Diazepam • Estazolam • Flurazepam • Lorazepam • Midazolam • Oxazepam • Quazepam • Temazepam • Triazolam	Bind to specific $GABA_A$ receptor subunits at central nervous system (CNS) neuronal synapses facilitating frequency of GABA-mediated chloride ion channel opening—enhance membrane hyperpolarization	Dose-dependent depressant effects on the CNS including sedation and relief of anxiety • amnesia • hypnosis • anesthesia • coma and respiratory depression	Acute anxiety states • panic attacks • generalized anxiety disorder • insomnia and other sleep disorders • relaxation of skeletal muscle • anesthesia (adjunctive) • seizure disorders	Half-lives from 2–40 h • oral activity • Hepatic metabolism—some active metabolites • *Toxicity:* Extensions of CNS depressant effects • dependence liability • *Interactions:* Additive CNS depression with ethanol and many other drugs
BENZODIAZEPINE ANTAGONIST				
• Flumazenil	Antagonist at benzodiazepine binding sites on the $GABA_A$ receptor	Blocks actions of benzodiazepines and zolpidem but not other sedative-hypnotic drugs	Management of benzodiazepine overdose	IV • short half-life • *Toxicity:* Agitation • confusion • possible withdrawal symptoms in benzodiazepine dependence
BARBITURATES				
• Amobarbital • Butabarbital • Mephobarbital • Pentobarbital • Phenobarbital • Secobarbital	Bind to specific $GABA_A$ receptor subunits at CNS neuronal synapses increasing duration of GABA-mediated chloride ion channel opening • enhance membrane hyperpolarization	Dose-dependent depressant effects on the CNS including sedation and relief of anxiety • amnesia • hypnosis • anesthesia • coma and respiratory depression • steeper dose-response relationship than benzodiazepines	Anesthesia (thiopental) • insomnia (secobarbital) • seizure disorders (phenobarbital)	Half-lives from 4–60 h • oral activity • Hepatic metabolism—phenobarbital 20% renal elimination • *Toxicity:* Extensions of CNS depressant effects • dependence liability > benzodiazepines • *Interactions:* Additive CNS depression with ethanol and many other drugs • induction of hepatic drug-metabolizing enzymes
NEWER HYPNOTICS				
• Eszopiclone • Zaleplon • Zolpidem	Bind selectively to a subgroup of $GABA_A$ receptors, acting like benzodiazepines to enhance membrane hyperpolarization	Rapid onset of hypnosis with few amnestic effects or day-after psychomotor depression or somnolence	Sleep disorders, especially those categorized by difficulty in falling asleep	Oral activity • short half-lives • CYP substrates • *Toxicity:* Extensions of CNS depressant effects • dependence liability • *Interactions:* Additive CNS depression with ethanol and many other drugs
MELATONIN RECEPTOR AGONIST				
• Ramelteon	Activates MT_1 and MT_2 receptors in suprachiasmatic nuclei in the CNS	Rapid onset of sleep with minimal rebound insomnia or withdrawal symptoms	Sleep disorders, especially those categorized by difficulty in falling asleep • not a controlled substance	Oral activity • forms active metabolite via CYP1A2 • *Toxicity:* Dizziness • fatigue • endocrine changes • *Interactions:* Fluvoxamine inhibits metabolism
5-HT-RECEPTOR AGONIST				
• Buspirone	Mechanism uncertain: Partial agonist at 5-HT receptors but also affinity for D_2 receptors	Slow onset (1–2 weeks) of anxiolytic effects • minimal psychomotor impairment—no additive CNS depression with sedative-hypnotic drugs	Generalized anxiety states	Oral activity • forms active metabolite • short half-life • *Toxicity:* Tachycardia • paresthesias • gastrointestinal distress • *Interactions:* CYP3A4 inducers and inhibitors

PREPARATIONS AVAILABLE

BENZODIAZEPINES

Alprazolam (generic, Xanax)
Oral: 0.25, 0.5, 1, 2 mg tablets, extended-release tablets, and orally disintegrating tablets; 1.0 mg/mL solution

Chlordiazepoxide (generic, Librium)
Oral: 5, 10, 25 mg capsules

Clorazepate (generic, Tranxene)
Oral: 3.75, 7.5, 15 mg tablets and capsules
Oral sustained-release: 11.25, 22.5 mg tablets

Clonazepam (generic, Klonopin)
Oral: 0.5, 1, 2 mg tablets; 0.125, 0.25, 0.5, 1, 2 mg orally disintegrating tablets

Diazepam (generic, Valium)
Oral: 2, 5, 10 mg tablets; 1, 5 mg/mL solutions
Parenteral: 5 mg/mL for injection

Estazolam (generic, ProSom)
Oral: 1, 2 mg tablets

Flurazepam (generic, Dalmane)
Oral: 15, 30 mg capsules

Lorazepam (generic, Ativan)
Oral: 0.5, 1, 2 mg tablets; 2 mg/mL solution
Parenteral: 2, 4 mg/mL for injection

Midazolam (Versed)
Oral: 2 mg/mL syrup
Parenteral: 1, 5 mg/mL in 1, 2, 5, 10 mL vials for injection

Oxazepam (generic)
Oral: 10, 15, 30 mg capsules

Quazepam (Doral)
Oral: 7.5, 15 mg tablets

Temazepam (generic, Restoril)
Oral: 7.5, 15, 22.5, 30 mg capsules

Triazolam (generic, Halcion)
Oral: 0.125, 0.25 mg tablets

BENZODIAZEPINE ANTAGONIST

Flumazenil (generic, Romazicon)
Parenteral: 0.1 mg/mL for IV injection

BARBITURATES

Amobarbital (Amytal)
Parenteral: powder in 250, 500 mg vials to reconstitute for injection

Mephobarbital (Mebaral)
Oral: 32, 50, 100 mg tablets

Pentobarbital (generic, Nembutal Sodium)
Oral: 50, 100 mg capsules; 4 mg/mL elixir
Rectal: 30, 60, 120, 200 mg suppositories
Parenteral: 50 mg/mL for injection

Phenobarbital (generic, Luminal Sodium)
Oral: 15, 16, 30, 60, 90, 100 mg tablets; 16 mg capsules; 15, 20 mg/5 mL elixirs
Parenteral: 30, 60, 65, 130 mg/mL for injection

Secobarbital (generic, Seconal)
Oral: 100 mg capsules

MISCELLANEOUS DRUGS

Buspirone (generic, BuSpar)
Oral: 5, 7.5, 10, 15, 30 mg tablets

Chloral hydrate (generic, Aquachloral Supprettes)
Oral: 500 mg capsules; 250, 500 mg/5 mL syrups
Rectal: 324, 648 mg suppositories

Eszopiclone (Lunesta)
Oral: 1, 2, 3 mg tablets

Hydroxyzine (generic, Atarax, Vistaril)
Oral: 10, 25, 50, 100 mg tablets; 25, 50, 100 mg capsules; 10 mg/5 mL syrup; 25 mg/5 mL suspension
Parenteral: 25, 50 mg/mL for injection

Meprobamate (generic, Equanil, Miltown)
Oral: 200, 400 mg tablets

Paraldehyde (generic)
Oral, rectal liquids: 1 g/mL

Ramelteon (Rozerem)
Oral: 8 mg tablets

Zaleplon (Sonata)
Oral: 5, 10 mg capsules

Zolpidem (generic, Ambien, Ambien-CR)
Oral: 5, 10 mg tablets; 6.25, 12.5 mg extended-release tablets

REFERENCES

Budur K et al: Advances in treating insomnia. Cleve Clin J Med 2007;74:251.

Chouinard G: Issues in the clinical use of benzodiazepines: Potency, withdrawal, and rebound. J Clin Psychiatry 2004;65(Suppl 5):7.

Clayton T et al: An updated unified pharmacophore model of the benzodiazepine binding site on gamma-aminobutyric acid(a) receptors: Correlation with comparative models. Curr Med Chem 2007;14:2755.

Cloos JM, Ferreira V: Current use of benzodiazepines in anxiety disorders. Curr Opin Psychiatry 2009;22:90.

Da Settimo F et al: GABA A/Bz receptor subtypes as targets for selective drugs. Curr Med Chem 2007;14:2680.

Drover DR: Comparative pharmacokinetics and pharmacodynamics of short-acting hypnosedatives: Zaleplon, zolpidem and zopiclone. Clin Pharmacokinet 2004;43:227.

Hanson SM, Czajkowski C: Structural mechanisms underlying benzodiazepine modulation of the GABA(A) receptor. J Neurosci 2008;28:3490.

Lader M et al: Withdrawing benzodiazepines in primary care. CNS Drugs 2009;23:19.

Miyamoto M: Pharmacology of ramelteon, a selective MT1/MT2 receptor agonist: A novel therapeutic drug for sleep disorders. CNS Neurosci Ther 2009;15:32.

Morin AK et al: Therapeutic options for sleep-maintenance and sleep-onset insomnia. Pharmacotherapy 2007;27:89.

Najib J: Eszopiclone, a nonbenzodiazepine sedative-hypnotic for the treatment of transient and chronic insomnia. Clin Ther 2006;28:491.

Neubauer DN: New directions in the pharmacologic treatment of insomnia. Primary Psychiatry 2006;13:51.

Ramakrishnan K et al: Treatment options for insomnia. Am Fam Physician 2007;76:526.

Rudolph U, Mohler H: GABA-based therapeutic approaches: $GABA_A$ receptor subtype functions. Curr Opin Pharmacol 2006;6:18.

Sanger DJ. The pharmacology and mechanism of action of new generation, non-benzodiazepine hypnotic agents. CNS Drugs 2004;18(Suppl 1):9.

Schutte-Rodin S et al: Clinical guideline for the evaluation and management of chronic insomnia in adults. J Clin Sleep Med 2008;4:487.

Simpson D, Curran MP: Ramelteon: A review of its use in insomnia. Drugs 2008:68:1901.

Siriwardena AN et al: Magic bullets for insomnia? Patient's use and experiences of newer (Z drugs) versus older (benzodiazepine) hypnotics for sleep problems in primary care. Br J Gen Pract 2008;58:417.

Verster JC et al: Residual effects of sleep medication on driving ability. Sleep Med Rev 2004;8:309.

CASE STUDY ANSWER

Common etiologies of insomnia include **situational** (eg, work or financial stress, interpersonal conflict), **medical** (eg, asthma, chronic pain), **psychiatric** (eg, mood, anxiety disorders), and **drug-induced** (eg, diuretics, steroids, stimulants). Such aspects of the patient's history would be of value in determining an appropriate course of action. For example, reducing this patient's consumption of diet cola (which commonly contains caffeine) might be of clinical value, as could nonpharmacologic approaches including stimulus control and sleep hygiene procedures. In terms of drug therapy (short term if possible), the pharmacokinetics of zolpidem and eszopiclone (but not zaleplon) are appropriate for a patient who has trouble both in falling asleep and staying asleep. Both drugs exhibit minimal next-day psychomotor performance or rebound insomnia on discontinuance.

CHAPTER 23

The Alcohols

Susan B. Masters, PhD

CASE STUDY

An 18-year-old college freshman began drinking alcohol at 8:30 PM during a hazing event at his new fraternity. Between 8:30 and approximately midnight, he and several other pledges consumed beer and a bottle of whiskey, and then he consumed most of a bottle of rum at the urging of upperclassmen. The young man complained of feeling nauseated, lay down on a couch, and began to lose consciousness. Two upperclassmen carried him to his bedroom, placed him on his stomach, and positioned a trash can nearby. Approximately 10 minutes later, the freshman was found unconscious and covered with vomit. There was a delay in treatment because the upperclassmen called the college police instead of calling 911. After the call was transferred to 911, emergency medical technicians responded quickly and discovered that the young man was not breathing and that he had choked on his vomit. He was rushed to the hospital, where he remained in a coma for 2 days before ultimately being pronounced dead. The patient's blood alcohol concentration shortly after arriving at the hospital was 510 mg/dL. What was the cause of this patient's death? If he had received medical care sooner, what treatment might have prevented his death?

Alcohol, primarily in the form of ethyl alcohol (ethanol), has occupied an important place in the history of humankind for at least 8000 years. In Western society, beer and wine were a main staple of daily life until the 19th century. These relatively dilute alcoholic beverages were preferred over water, which was known to be associated with acute and chronic illness. They provided important calories and nutrients and served as a main source of daily liquid intake. As systems for improved sanitation and water purification were introduced in the 1800s, beer and wine became less important components of the human diet, and the consumption of alcoholic beverages, including distilled preparations with higher concentrations of alcohol, shifted toward their present-day role, in many societies, as a socially acceptable form of recreation.

Today, alcohol is widely consumed. Like other sedative-hypnotic drugs, alcohol in low to moderate amounts relieves anxiety and fosters a feeling of well-being or even euphoria. However, alcohol is also the most commonly abused drug in the world, and the cause of vast medical and societal costs. In the United States, approximately 75% of the adult population drinks alcohol regularly. The majority of this drinking population is able to enjoy the pleasurable effects of alcohol without allowing alcohol consumption to become a health risk. However, about 8% of the general population in the United States has an **alcohol-use disorder.** Individuals who use alcohol in dangerous situations (eg, drinking and driving or combining alcohol with other medications) or continue to drink alcohol in spite of adverse consequences related directly to their alcohol consumption suffer from **alcohol abuse.** Individuals with **alcohol dependence** have characteristics of alcohol abuse and additionally exhibit physical dependence on alcohol (tolerance to alcohol and signs and symptoms upon withdrawal). They also demonstrate an inability to control their drinking and devote much time to getting and using alcohol, or recovering from its effects. The alcohol-use disorders are complex, with genetic as well as environmental determinants.

The societal and medical costs of alcohol abuse are staggering. It is estimated that about 30% of all people admitted to hospitals have coexisting alcohol problems. Once in the hospital, people with chronic alcoholism generally have poorer outcomes. In addition, each year tens of thousands of children are born with morphologic and functional defects resulting from prenatal exposure to ethanol. Despite the investment of many resources and much basic research, alcoholism remains a common chronic disease that is difficult to treat.

Ethanol and many other alcohols with potentially toxic effects are used as fuels and in industry—some in enormous quantities. In addition to ethanol, methanol and ethylene glycol toxicity occurs with sufficient frequency to warrant discussion in this chapter.

BASIC PHARMACOLOGY OF ETHANOL

Pharmacokinetics

Ethanol is a small water-soluble molecule that is absorbed rapidly from the gastrointestinal tract. After ingestion of alcohol in the fasting state, peak blood alcohol concentrations are reached within 30 minutes. The presence of food in the stomach delays absorption by slowing gastric emptying. Distribution is rapid, with tissue levels approximating the concentration in blood. The volume of distribution for ethanol approximates total body water (0.5–0.7 L/kg). For an equivalent oral dose of alcohol, women have a higher peak concentration than men, in part because women have a lower total body water content and in part because of differences in first-pass metabolism. In the central nervous system (CNS), the concentration of ethanol rises quickly, since the brain receives a large proportion of total blood flow and ethanol readily crosses biologic membranes.

Over 90% of alcohol consumed is oxidized in the liver; much of the remainder is excreted through the lungs and in the urine. The excretion of a small but consistent proportion of alcohol by the lungs can be quantified with breath alcohol tests that serve as a basis for a legal definition of "driving under the influence" in many countries. At levels of ethanol usually achieved in blood, the rate of oxidation follows zero-order kinetics; that is, it is independent of time and concentration of the drug. The typical adult can metabolize 7–10 g (150–220 mmol) of alcohol per hour, the equivalent of approximately one "drink" [10 oz (300 mL) beer, 3.5 oz (105 mL) wine, or 1 oz (30 mL) distilled 80-proof spirits].

Two major pathways of alcohol metabolism to acetaldehyde have been identified (Figure 23–1). Acetaldehyde is then oxidized to acetate by a third metabolic process.

A. Alcohol Dehydrogenase Pathway

The primary pathway for alcohol metabolism involves alcohol dehydrogenase (ADH), a family of cytosolic enzymes that catalyze the conversion of alcohol to acetaldehyde (Figure 23–1, left). These enzymes are located mainly in the liver, but small amounts are found in other organs such as the brain and stomach. There is considerable genetic variation in ADH enzymes, affecting the rate of ethanol metabolism and also appearing to alter vulnerability to alcohol-abuse disorders. For example, one ADH allele (the *ADH1B*2* allele), which is associated with rapid conversion of ethanol to acetaldehyde, has been found to be protective against alcohol dependence in several ethnic populations and especially East Asians.

Some metabolism of ethanol by ADH occurs in the stomach in men, but a smaller amount occurs in women, who appear to have lower levels of the gastric enzyme. This difference in gastric metabolism of alcohol in women probably contributes to the sex-related differences in blood alcohol concentrations noted above.

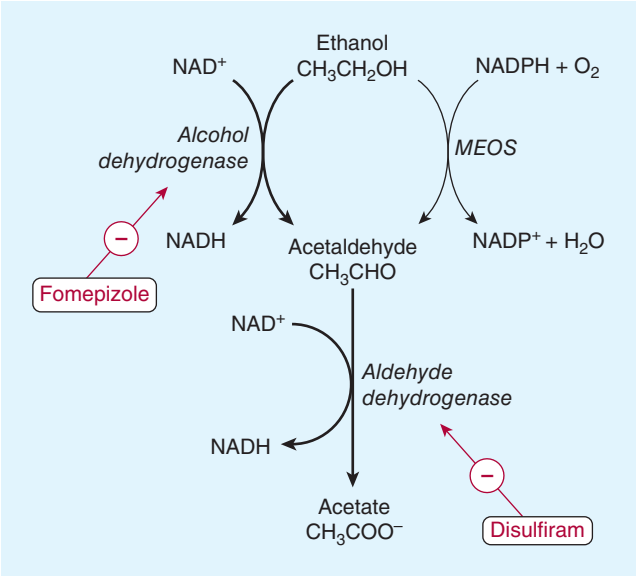

FIGURE 23–1 Metabolism of ethanol by alcohol dehydrogenase and the microsomal ethanol-oxidizing system (MEOS). Alcohol dehydrogenase and aldehyde dehydrogenase are inhibited by fomepizole and disulfiram, respectively. NAD^+, nicotinamide adenine dinucleotide; NADPH, nicotinamide adenine dinucleotide phosphate.

During conversion of ethanol by ADH to acetaldehyde, hydrogen ion is transferred from ethanol to the cofactor nicotinamide adenine dinucleotide (NAD^+) to form NADH. As a net result, alcohol oxidation generates an excess of reducing equivalents in the liver, chiefly as NADH. The excess NADH production appears to contribute to the metabolic disorders that accompany chronic alcoholism and to both the lactic acidosis and hypoglycemia that frequently accompany acute alcohol poisoning.

B. Microsomal Ethanol-Oxidizing System (MEOS)

This enzyme system, also known as the mixed function oxidase system, uses NADPH as a cofactor in the metabolism of ethanol (Figure 23–1, right) and consists primarily of cytochrome P450 2E1, 1A2, and 3A4 (see Chapter 4).

During chronic alcohol consumption, MEOS activity is induced. As a result, chronic alcohol consumption results in significant increases not only in ethanol metabolism but also in the clearance of other drugs eliminated by the cytochrome P450s that constitute the MEOS system, and in the generation of the toxic byproducts of cytochrome P450 reactions (toxins, free radicals, H_2O_2).

C. Acetaldehyde Metabolism

Much of the acetaldehyde formed from alcohol is oxidized in the liver in a reaction catalyzed by mitochondrial NAD-dependent aldehyde dehydrogenase (ALDH). The product of this reaction is acetate (Figure 23–1), which can be further metabolized to CO_2 and water, or used to form acetyl-CoA.

Oxidation of acetaldehyde is inhibited by **disulfiram,** a drug that has been used to deter drinking by patients with alcohol dependence. When ethanol is consumed in the presence of disulfiram, acetaldehyde accumulates and causes an unpleasant reaction of facial flushing, nausea, vomiting, dizziness, and headache. Several other drugs (eg, metronidazole, cefotetan, trimethoprim) inhibit ALDH and can cause a disulfiram-like reaction if combined with ethanol.

Some people, primarily of East Asian descent, have genetic deficiency in the activity of the mitochondrial form of ALDH, which is encoded by the *ALDH2* gene. When these individuals drink alcohol, they develop high blood acetaldehyde concentrations and experience a noxious reaction similar to that seen with the combination of disulfiram and ethanol. This form of ALDH, with reduced activity, is strongly protective against alcohol-use disorders.

Pharmacodynamics of Acute Ethanol Consumption

A. Central Nervous System

The CNS is markedly affected by acute alcohol consumption. Alcohol causes sedation, relief of anxiety and, at higher concentrations, slurred speech, ataxia, impaired judgment, and disinhibited behavior, a condition usually called intoxication or drunkenness (Table 23–1). These CNS effects are most marked as the blood level is rising, because acute tolerance to the effects of alcohol occurs after a few hours of drinking. For chronic drinkers who are tolerant to the effects of alcohol, higher concentrations are needed to elicit these CNS effects. For example, an individual with chronic alcoholism may appear sober or only slightly intoxicated with a blood alcohol concentration of 300–400 mg/dL, whereas this level is associated with marked intoxication or even coma in a nontolerant individual. The propensity of moderate doses of alcohol to inhibit the attention and information-processing skills as well as the motor skills required for operation of motor vehicles has profound effects. Approximately 30–40% of all traffic accidents resulting in a fatality in the United States involve at least one person with blood alcohol near or above the legal level of intoxication, and drunken driving is a leading cause of death in young adults.

TABLE 23–1 Blood alcohol concentration (BAC) and clinical effects in nontolerant individuals.

BAC (mg/dL)[1]	Clinical Effect
50–100	Sedation, subjective "high," slower reaction times
100–200	Impaired motor function, slurred speech, ataxia
200–300	Emesis, stupor
300–400	Coma
> 400	Respiratory depression, death

[1]In many parts of the United States, a blood level above 80–100 mg/dL for adults or 5–20 mg/dL for persons under 21 is sufficient for conviction of driving while "under the influence."

Like other sedative-hypnotic drugs, alcohol is a CNS depressant. At high blood concentrations, it induces coma, respiratory depression, and death.

Ethanol affects a large number of membrane proteins that participate in signaling pathways, including neurotransmitter receptors for amines, amino acids, opioids, and neuropeptides; enzymes such as Na^+/K^+-ATPase, adenylyl cyclase, phosphoinositide-specific phospholipase C; a nucleoside transporter; and ion channels. Much attention has focused on alcohol's effects on neurotransmission by glutamate and γ-aminobutyric acid (GABA), the main excitatory and inhibitory neurotransmitters in the CNS. Acute ethanol exposure enhances the action of GABA at $GABA_A$ receptors, which is consistent with the ability of GABA-mimetics to intensify many of the acute effects of alcohol and of $GABA_A$ antagonists to attenuate some of the actions of ethanol. Ethanol inhibits the ability of glutamate to open the cation channel associated with the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptors. The NMDA receptor is implicated in many aspects of cognitive function, including learning and memory. "Blackouts"—periods of memory loss that occur with high levels of alcohol—may result from inhibition of NMDA receptor activation. Experiments that use modern genetic approaches eventually will yield a more precise definition of ethanol's direct and indirect targets. In recent years, experiments with mutant strains of mice, worms, and flies have reinforced the importance of previously identified targets and helped identify new candidates, including a calcium-regulated and voltage-gated potassium channel that may be one of ethanol's direct targets (see Box: What Can Drunken Worms, Flies, and Mice Tell Us about Alcohol?).

B. Heart

Significant depression of myocardial contractility has been observed in individuals who acutely consume moderate amounts of alcohol, ie, at a blood concentration above 100 mg/dL.

C. Smooth Muscle

Ethanol is a vasodilator, probably as a result of both CNS effects (depression of the vasomotor center) and direct smooth muscle relaxation caused by its metabolite, acetaldehyde. In cases of severe overdose, hypothermia—caused by vasodilation—may be marked in cold environments. Ethanol also relaxes the uterus and—before the introduction of more effective and safer uterine relaxants (eg, calcium channel antagonists)—was used intravenously for the suppression of premature labor.

Consequences of Chronic Alcohol Consumption

Chronic alcohol consumption profoundly affects the function of several vital organs—particularly the liver—and the nervous, gastrointestinal, cardiovascular, and immune systems. Since ethanol has low potency, it requires concentrations thousands of times higher than other misused drugs (eg, cocaine, opiates, amphetamines) to produce its intoxicating effects. As a result, ethanol is consumed in quantities that are unusually large for a pharmacologically active

What Can Drunken Worms, Flies, and Mice Tell Us about Alcohol?

For a drug like ethanol, which exhibits low potency and specificity, and modifies complex behaviors, the precise roles of its many direct and indirect targets are difficult to define. Increasingly, ethanol researchers are employing genetic approaches to complement standard neurobiologic experimentation. Three experimental animal systems for which powerful genetic techniques exist—mice, flies, and worms—have yielded intriguing results.

Strains of mice with abnormal sensitivity to ethanol were identified many years ago by breeding and selection programs. Using sophisticated genetic mapping and sequencing techniques, researchers have made progress in identifying the genes that confer these traits. A more targeted approach is the use of transgenic mice to test hypotheses about specific genes. For example, after earlier experiments suggested a link between brain neuropeptide Y (NPY) and ethanol, researchers used two transgenic mouse models to further investigate the link. They found that a strain of mice that lacks the gene for NPY—NPY knockout mice—consume more ethanol than control mice and are less sensitive to ethanol's sedative effects. As would be expected if increased concentrations of NPY in the brain make mice more sensitive to ethanol, a strain of mice that overexpresses NPY drinks less alcohol than the controls even though their total consumption of food and liquid is normal. Work with other transgenic knockout mice supports the central role in ethanol responses of signaling molecules that have long been believed to be involved (eg, $GABA_A$, glutamate, dopamine, opioid, and serotonin receptors) and has helped build the case for newer candidates such as NPY and corticotropin-releasing hormone, cannabinoid receptors, ion channels, and protein kinase C.

It is easy to imagine mice having measurable behavioral responses to alcohol, but drunken worms and fruit flies are harder to imagine. Actually, both invertebrates respond to ethanol in ways that parallel mammalian responses. *Drosophila melanogaster* fruit flies exposed to ethanol vapor show increased locomotion at low concentrations but at higher concentrations, become poorly coordinated, sedated, and finally immobile. These behaviors can be monitored by sophisticated laser or video tracking methods or with an ingenious "chromatography" column that separates relatively insensitive flies from inebriated flies, which drop to the bottom of the column. The worm *Caenorhabditis elegans* similarly exhibits increased locomotion at low ethanol concentrations and, at higher concentrations, reduced locomotion, sedation, and—something that can be turned into an effective screen for mutant worms that are resistant to ethanol—impaired egg laying. The advantage of using flies and worms as genetic models for ethanol research is their relatively simple neuroanatomy, well-established techniques for genetic manipulation, an extensive library of well-characterized mutants, and completely or nearly completely solved genetic codes. Already, much information has accumulated about candidate proteins involved with the effects of ethanol in flies. In an elegant study on *C elegans,* researchers found evidence that a calcium-activated, voltage-gated BK potassium channel is a direct target of ethanol. This channel, which is activated by ethanol, has close homologs in flies and vertebrates, and evidence is accumulating that ethanol has similar effects in these homologs. Genetic experiments in these model systems should provide information that will help narrow and focus research into the complex and important effects of ethanol in humans.

drug. The tissue damage caused by chronic alcohol ingestion results from a combination of the direct effects of ethanol and acetaldehyde, and the metabolic consequences of processing a heavy load of a metabolically active substance. Specific mechanisms implicated in tissue damage include increased oxidative stress coupled with depletion of glutathione, damage to mitochondria, growth factor dysregulation, and potentiation of cytokine-induced injury.

Chronic consumption of large amounts of alcohol is associated with an increased risk of death. Deaths linked to alcohol consumption are caused by liver disease, cancer, accidents, and suicide.

A. Liver and Gastrointestinal Tract

Liver disease is the most common medical complication of alcohol abuse; an estimated 15–30% of chronic heavy drinkers eventually develop severe liver disease. Alcoholic fatty liver, a reversible condition, may progress to alcoholic hepatitis and finally to cirrhosis and liver failure. In the United States, chronic alcohol abuse is the leading cause of liver cirrhosis and of the need for liver transplantation. The risk of developing liver disease is related both to the average amount of daily consumption and to the duration of alcohol abuse. Women appear to be more susceptible to alcohol hepatotoxicity than men. Concurrent infection with hepatitis B or C virus increases the risk of severe liver disease.

The pathogenesis of alcoholic liver disease is a multifactorial process involving metabolic repercussions of ethanol oxidation in the liver, dysregulation of fatty acid oxidation and synthesis, and activation of the innate immune system by a combination of direct effects of ethanol and its metabolites and by bacterial endotoxins that access the liver as a result of ethanol-induced changes in the intestinal tract. Tumor necrosis factor-α, a proinflammatory cytokine that is consistently elevated in animal models of alcoholic liver disease and in patients with alcoholic liver disease, appears to play a pivotal role in the progression of alcoholic liver disease and may be a fruitful therapeutic target.

Other portions of the gastrointestinal tract can also be injured. Chronic alcohol ingestion is by far the most common cause of chronic pancreatitis in the Western world. In addition to its direct toxic effect on pancreatic acinar cells, alcohol alters pancreatic epithelial permeability and promotes the formation of protein plugs and calcium carbonate-containing stones.

Individuals with chronic alcoholism are prone to gastritis and have increased susceptibility to blood and plasma protein loss during drinking, which may contribute to anemia and protein malnutrition. Alcohol also injures the small intestine, leading to diarrhea, weight loss, and multiple vitamin deficiencies.

Malnutrition from dietary deficiency and vitamin deficiencies due to malabsorption are common in alcoholism. Malabsorption of water-soluble vitamins is especially severe.

B. Nervous System

1. Tolerance and dependence—The consumption of alcohol in high doses over a long period results in tolerance and in physical and psychological dependence. Tolerance to the intoxicating effects of alcohol is a complex process involving poorly understood changes in the nervous system as well as the metabolic changes described earlier. As with other sedative-hypnotic drugs, there is a limit to tolerance, so that only a relatively small increase in the lethal dose occurs with increasing alcohol use.

Chronic alcohol drinkers, when forced to reduce or discontinue alcohol, experience a withdrawal syndrome, which indicates the existence of physical dependence. Alcohol withdrawal symptoms classically consist of hyperexcitability in mild cases and seizures, toxic psychosis, and **delirium tremens** in severe ones. The dose, rate, and duration of alcohol consumption determine the intensity of the withdrawal syndrome. When consumption has been very high, merely reducing the rate of consumption may lead to signs of withdrawal.

Psychological dependence on alcohol is characterized by a compulsive desire to experience the rewarding effects of alcohol and, for current drinkers, a desire to avoid the negative consequences of withdrawal. People who have recovered from alcoholism and become abstinent still experience periods of intense craving for alcohol that can be triggered by environmental cues associated in the past with drinking, such as familiar places, groups of people, or events.

The molecular basis of alcohol tolerance and dependence is not known with certainty, nor is it known whether the two phenomena reflect opposing effects on a shared molecular pathway. Tolerance may result from ethanol-induced up-regulation of a pathway in response to the continuous presence of ethanol. Dependence may result from overactivity of that same pathway after the ethanol effect dissipates and before the system has time to return to a normal ethanol-free state.

Chronic exposure of animals or cultured cells to alcohol elicits a multitude of adaptive responses involving neurotransmitters and their receptors, ion channels, and enzymes that participate in signal transduction pathways. Up-regulation of the NMDA subtype of glutamate receptors and voltage-sensitive Ca^{2+} channels may underlie the seizures that accompany the alcohol withdrawal syndrome. Based on the ability of sedative-hypnotic drugs that enhance GABAergic neurotransmission to substitute for alcohol during alcohol withdrawal and evidence of down-regulation of $GABA_A$-mediated responses with chronic alcohol exposure, changes in GABA neurotransmission are believed to play a central role in tolerance and withdrawal.

Like other drugs of abuse, ethanol modulates neural activity in the brain's mesolimbic dopamine reward circuit and increases dopamine release in the nucleus accumbens (see Chapter 32). Alcohol affects local concentrations of serotonin, opioids, and dopamine—neurotransmitters involved in the brain reward system—and has complex effects on the expression of receptors for these neurotransmitters and their signaling pathways. The discovery that naltrexone, a nonselective opioid receptor antagonist, helps patients who are recovering from alcoholism abstain from drinking supports the idea that a common neurochemical reward system is shared by very different drugs associated with physical and psychological dependence. There is also convincing evidence from animal models that ethanol intake and seeking behavior are reduced by antagonists of another important regulator of the brain reward system, the cannabinoid CB1 receptor, which is the molecular target of active ingredients in marijuana. Two other important neuroendocrine systems that appear to play key roles in modulating ethanol-seeking activity in experimental animals are the appetite-regulating system—which uses peptides such as leptin, ghrelin, and neuropeptide Y—and the stress response system, which is controlled by corticotropin-releasing factor.

2. Neurotoxicity—Consumption of large amounts of alcohol over extended periods (usually years) often leads to neurologic deficits. The most common neurologic abnormality in chronic alcoholism is generalized symmetric peripheral nerve injury, which begins with distal paresthesias of the hands and feet. Degenerative changes can also result in gait disturbances and ataxia. Other neurologic disturbances associated with alcoholism include dementia and, rarely, demyelinating disease.

Wernicke-Korsakoff syndrome is a relatively uncommon but important entity characterized by paralysis of the external eye muscles, ataxia, and a confused state that can progress to coma and death. It is associated with thiamine deficiency but is rarely seen in the absence of alcoholism. Because of the importance of thiamine in this pathologic condition and the absence of toxicity associated with thiamine administration, all patients suspected of having Wernicke-Korsakoff syndrome (including virtually all patients who present to the emergency department with altered consciousness, seizures, or both) should receive thiamine therapy. Often, the ocular signs, ataxia, and confusion improve promptly upon administration of thiamine. However, most patients are left with a chronic disabling memory disorder known as Korsakoff's psychosis.

Alcohol may also impair visual acuity, with painless blurring that occurs over several weeks of heavy alcohol consumption. Changes are usually bilateral and symmetric and may be followed by optic nerve degeneration. Ingestion of ethanol substitutes such as methanol (see Pharmacology of Other Alcohols) causes severe visual disturbances.

C. Cardiovascular System

1. Cardiomyopathy and heart failure—Alcohol has complex effects on the cardiovascular system. Heavy alcohol consumption of long duration is associated with a dilated cardiomyopathy with ventricular hypertrophy and fibrosis. In animals and humans, alcohol induces a number of changes in heart cells that may contribute to cardiomyopathy. They include membrane disruption, depressed function of mitochondria and sarcoplasmic reticulum,

intracellular accumulation of phospholipids and fatty acids, and up-regulation of voltage-gated calcium channels. There is evidence that patients with alcohol-induced dilated cardiomyopathy do significantly worse than patients with idiopathic dilated cardiomyopathy, even though cessation of drinking is associated with a reduction in cardiac size and improved function. The poorer prognosis for patients who continue to drink appears to be due in part to interference by ethanol with the beneficial effects of β blockers and angiotensin-converting enzyme (ACE) inhibitors.

2. Arrhythmias—Heavy drinking—and especially "binge" drinking—are associated with both atrial and ventricular arrhythmias. Patients undergoing alcohol withdrawal syndrome can develop severe arrhythmias that may reflect abnormalities of potassium or magnesium metabolism as well as enhanced release of catecholamines. Seizures, syncope, and sudden death during alcohol withdrawal may be due to these arrhythmias.

3. Hypertension—A link between heavier alcohol consumption (more than three drinks per day) and hypertension has been firmly established in epidemiologic studies. Alcohol is estimated to be responsible for approximately 5% of cases of hypertension, making it one of the most common causes of reversible hypertension. This association is independent of obesity, salt intake, coffee drinking, and cigarette smoking. A reduction in alcohol intake appears to be effective in lowering blood pressure in hypertensives who are also heavy drinkers; the hypertension seen in this population is also responsive to standard blood pressure medications.

4. Coronary heart disease—Although the deleterious effects of excessive alcohol use on the cardiovascular system are well established, there is strong epidemiologic evidence that moderate alcohol consumption actually prevents coronary heart disease (CHD), ischemic stroke, and peripheral arterial disease. This type of relationship between mortality and the dose of a drug is called a "J-shaped" relationship. Results of these clinical studies are supported by ethanol's ability to raise serum levels of high-density lipoprotein (HDL) cholesterol (the form of cholesterol that appears to protect against atherosclerosis; see Chapter 35), by its ability to inhibit some of the inflammatory processes that underlie atherosclerosis while also increasing production of the endogenous anticoagulant tissue plasminogen activator (t-PA, see Chapter 34), and by the presence in alcoholic beverages (especially red wine) of antioxidants and other substances that may protect against atherosclerosis. These observational studies are intriguing, but randomized clinical trials examining the possible benefit of moderate alcohol consumption in prevention of CHD have not been carried out.

D. Blood

Alcohol indirectly affects hematopoiesis through metabolic and nutritional effects and may also directly inhibit the proliferation of all cellular elements in bone marrow. The most common hematologic disorder seen in chronic drinkers is mild anemia resulting from alcohol-related folic acid deficiency. Iron deficiency anemia may result from gastrointestinal bleeding. Alcohol has also been implicated as a cause of several hemolytic syndromes, some of which are associated with hyperlipidemia and severe liver disease.

E. Endocrine System and Electrolyte Balance

Chronic alcohol use has important effects on the endocrine system and on fluid and electrolyte balance. Clinical reports of gynecomastia and testicular atrophy in alcoholics with or without cirrhosis suggest a derangement in steroid hormone balance.

Individuals with chronic liver disease may have disorders of fluid and electrolyte balance, including ascites, edema, and effusions. Alterations of whole body potassium induced by vomiting and diarrhea, as well as severe secondary aldosteronism, may contribute to muscle weakness and can be worsened by diuretic therapy. The metabolic derangements caused by metabolism of large amounts of ethanol can result in hypoglycemia, as a result of impaired hepatic gluconeogenesis, and in ketosis, caused by excessive lipolytic factors, especially increased cortisol and growth hormone.

F. Fetal Alcohol Syndrome

Chronic maternal alcohol abuse during pregnancy is associated with teratogenic effects, and alcohol is a leading cause of mental retardation and congenital malformation. The abnormalities that have been characterized as fetal alcohol syndrome include (1) intrauterine growth retardation, (2) microcephaly, (3) poor coordination, (4) underdevelopment of midfacial region (appearing as a flattened face), and (5) minor joint anomalies. More severe cases may include congenital heart defects and mental retardation. Although the level of alcohol intake required to cause serious neurologic deficits appears quite high, the threshold for more subtle neurologic deficits is uncertain.

The mechanisms that underlie ethanol's teratogenic effects are unknown. Ethanol rapidly crosses the placenta and reaches concentrations in the fetus that are similar to those in maternal blood. The fetal liver has little or no alcohol dehydrogenase activity, so the fetus must rely on maternal and placental enzymes for elimination of alcohol.

The neuropathologic abnormalities seen in humans and in animal models of fetal alcohol syndrome indicate that ethanol triggers apoptotic neurodegeneration and also causes aberrant neuronal and glial migration in the developing nervous system. In tissue culture systems, ethanol causes a striking reduction in neurite outgrowth.

G. Immune System

The effects of alcohol on the immune system are complex; immune function in some tissues is inhibited (eg, the lung), whereas pathologic, hyperactive immune function in other tissues is triggered (eg, liver, pancreas). In addition, acute and chronic exposure to alcohol have widely different effects on immune function. The types of immunologic changes reported for the lung include suppression of the function of alveolar macrophages, inhibition of chemotaxis of granulocytes, and reduced number and function of T cells. In the liver, there is enhanced function of key cells of the innate immune system (eg, Kupffer cells, hepatic stellate cells) and increased cytokine production. In addition to the inflammatory damage that chronic heavy alcohol use precipitates in the liver and pancreas, it predisposes to infections, especially of

the lung, and worsens the morbidity and increases the mortality risk of patients with pneumonia.

H. Increased Risk of Cancer

Chronic alcohol use increases the risk for cancer of the mouth, pharynx, larynx, esophagus, and liver. Evidence also points to a small increase in the risk of breast cancer in women. Much more information is required before a threshold level for alcohol consumption as it relates to cancer can be established. Alcohol itself does not appear to be a carcinogen in most test systems. However, its primary metabolite, acetaldehyde, can damage DNA, as can the reactive oxygen species produced by increased cytochrome P450 activity. Other factors implicated in the link between alcohol and cancer include changes in folate metabolism and the growth-promoting effects of chronic inflammation.

Alcohol-Drug Interactions

Interactions between ethanol and other drugs can have important clinical effects resulting from alterations in the pharmacokinetics or pharmacodynamics of the second drug.

The most common pharmacokinetic alcohol-drug interactions stem from alcohol-induced increases of drug-metabolizing enzymes, as described in Chapter 4. Thus, prolonged intake of alcohol without damage to the liver can enhance the metabolic biotransformation of other drugs. Ethanol-mediated induction of hepatic cytochrome P450 enzymes is particularly important with regard to acetaminophen. Chronic consumption of three or more drinks per day increases the risk of hepatotoxicity due to toxic or even high therapeutic levels of acetaminophen as a result of increased P450-mediated conversion of acetaminophen to reactive hepatotoxic metabolites (see Figure 4–4). In 1998, the Food and Drug Administration (FDA) announced that all over-the-counter products containing acetaminophen must carry a warning about the relation between chronic ethanol consumption and acetaminophen-induced hepatotoxicity.

In contrast, *acute* alcohol use can inhibit metabolism of other drugs because of decreased enzyme activity or decreased liver blood flow. Phenothiazines, tricyclic antidepressants, and sedative-hypnotic drugs are the most important drugs that interact with alcohol by this pharmacokinetic mechanism.

Pharmacodynamic interactions are also of great clinical significance. The additive CNS depression that occurs when alcohol is combined with other CNS depressants, particularly sedative-hypnotics, is most important. Alcohol also potentiates the pharmacologic effects of many nonsedative drugs, including vasodilators and oral hypoglycemic agents.

■ CLINICAL PHARMACOLOGY OF ETHANOL

Alcohol is the cause of more preventable morbidity and mortality than all other drugs combined with the exception of tobacco. The search for specific etiologic factors or the identification of significant predisposing variables for alcohol abuse has generally led to disappointing results. Personality type, severe life stresses, psychiatric disorders, and parental role models are not reliable predictors of alcohol abuse. Although environmental factors clearly play a role, evidence suggests that there is a large genetic contribution to the development of alcoholism. Not surprisingly, polymorphisms in alcohol dehydrogenase and aldehyde dehydrogenase that lead to increased aldehyde accumulation and its associated facial flushing, nausea, and hypotension appear to protect against alcoholism. Much attention in genetic mapping experiments has focused on membrane-signaling proteins known to be affected by ethanol and on protein constituents of reward pathways in the brain. Polymorphisms associated with a relative insensitivity to alcohol and presumably thereby a greater risk of alcohol abuse have been identified in genes encoding an α subunit of the $GABA_A$ receptor, an M_2 muscarinic receptor, a serotonin transporter, adenylyl cyclase, and a potassium channel. The link between a polymorphism in an opioid receptor gene and a blunted response to naltrexone raises the possibility of genotype-guided pharmacotherapy for alcohol dependence.

MANAGEMENT OF ACUTE ALCOHOL INTOXICATION

Nontolerant individuals who consume alcohol in large quantities develop typical effects of acute sedative-hypnotic drug overdose along with the cardiovascular effects previously described (vasodilation, tachycardia) and gastrointestinal irritation. Since tolerance is not absolute, even individuals with chronic alcohol dependence may become severely intoxicated if sufficient alcohol is consumed.

The most important goals in the treatment of acute alcohol intoxication are to prevent severe respiratory depression and aspiration of vomitus. Even with very high blood ethanol levels, survival is probable as long as the respiratory and cardiovascular systems can be supported. The average blood alcohol concentration in fatal cases is above 400 mg/dL; however, the lethal dose of alcohol varies because of varying degrees of tolerance.

Electrolyte imbalances often need to be corrected and metabolic alterations may require treatment of hypoglycemia and ketoacidosis by administration of **glucose. Thiamine** is given to protect against Wernicke-Korsakoff syndrome. Patients who are dehydrated and vomiting should also receive electrolyte solutions. If vomiting is severe, large amounts of potassium may be required as long as renal function is normal.

MANAGEMENT OF ALCOHOL WITHDRAWAL SYNDROME

Abrupt alcohol discontinuation in an individual with alcohol dependence leads to a characteristic syndrome of motor agitation, anxiety, insomnia, and reduction of seizure threshold. The severity of the syndrome is usually proportionate to the degree and duration of alcohol abuse. However, this can be greatly modified by the use of other sedatives as well as by associated factors (eg, diabetes,

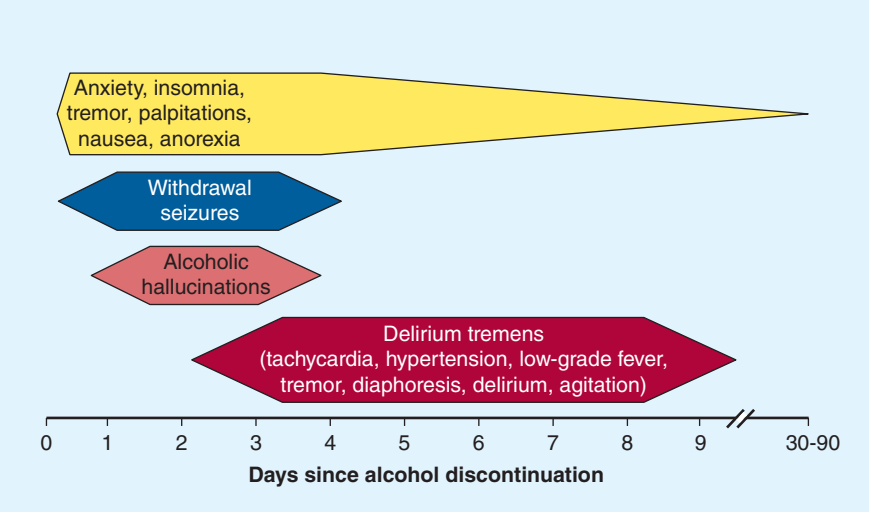

FIGURE 23–2 Time course of events during the alcohol withdrawal syndrome. The signs and symptoms that manifest earliest are anxiety, insomnia, tremor, palpitations, nausea, and anorexia as well as (in severe syndromes) hallucinations and seizures. Delirium tremens typically develops 48–72 hours after alcohol discontinuation. The earliest symptoms (anxiety, insomnia, etc) can persist, in a milder form, for several months after alcohol discontinuation.

injury). In its mildest form, the alcohol withdrawal syndrome of increased pulse and blood pressure, tremor, anxiety, and insomnia occurs 6–8 hours after alcohol consumption is stopped (Figure 23–2). These effects usually lessen in 1–2 days, although some such as anxiety and sleep disturbances can be seen at decreasing levels for several months. In some patients, more severe acute reactions occur, with patients at risk of withdrawal seizures or alcoholic hallucinations during the first 1–5 days of withdrawal. Alcohol withdrawal is one of the most common causes of seizures in adults. Several days later, individuals can develop the syndrome of delirium tremens, which is characterized by delirium, agitation, autonomic nervous system instability, low-grade fever, and diaphoresis.

The major objective of drug therapy in the alcohol withdrawal period is prevention of seizures, delirium, and arrhythmias. Potassium, magnesium, and phosphate balance should be restored as rapidly as is consistent with renal function. Thiamine therapy is initiated in all cases. Individuals in mild alcohol withdrawal do not need any other pharmacologic assistance.

Specific drug treatment for detoxification in more severe cases involves two basic principles: substituting a long-acting sedative-hypnotic drug for alcohol and then gradually reducing ("tapering") the dose of the long-acting drug. Because of their wide margin of safety, benzodiazepines are preferred. The choice of a specific agent in this class is generally based on pharmacokinetic or economic considerations. Long-acting benzodiazepines, including chlordiazepoxide and diazepam, have the advantage of requiring less frequent dosing. Since their pharmacologically active metabolites are eliminated slowly, the long-acting drugs provide a built-in tapering effect. A disadvantage of the long-acting drugs is that they and their active metabolites may accumulate, especially in patients with compromised liver function. Short-acting drugs such as lorazepam and oxazepam are rapidly converted to inactive water-soluble metabolites that will not accumulate, and for this reason the short-acting drugs are especially useful in alcoholic patients with liver disease. Benzodiazepines can be administered orally in mild or moderate cases, or parenterally for patients with more severe withdrawal reactions.

After the alcohol withdrawal syndrome has been treated acutely, sedative-hypnotic medications must be tapered slowly over several weeks. Complete detoxification is not achieved with just a few days of alcohol abstinence. Several months may be required for restoration of normal nervous system function, especially sleep.

TREATMENT OF ALCOHOLISM

After detoxification, psychosocial therapy either in intensive inpatient or in outpatient rehabilitation programs serves as the primary treatment for alcohol dependence. Other psychiatric problems, most commonly depressive or anxiety disorders, often coexist with alcoholism and, if untreated, can contribute to the tendency of detoxified alcoholics to relapse. Treatment for these associated disorders with counseling and drugs can help decrease the rate of relapse for alcoholic patients.

Three drugs—disulfiram, naltrexone, and acamprosate—have FDA approval for adjunctive treatment of alcohol dependence.

Naltrexone

Naltrexone, a relatively long-acting opioid antagonist, blocks the effects at μ opioid receptors (see Chapter 31). Studies in experimental animals first suggested a link between alcohol consumption and opioids. Injection of small amounts of opioids was followed by an increase in alcohol drinking, whereas administration of opioid antagonists inhibited self-administration of alcohol.

Naltrexone, both alone and in combination with behavioral counseling, has been shown in a number of short-term (12- to 16-week) placebo-controlled trials to reduce the rate of relapse to either drinking or alcohol dependence and to reduce craving for alcohol, especially in patients with high rates of naltrexone adherence. Naltrexone was approved in 1994 by the FDA for treatment of alcohol dependence.

Naltrexone is generally taken once a day in an oral dose of 50 mg for treatment of alcoholism. An extended-release formulation administered as an IM injection once every 4 weeks is also effective. The drug can cause dose-dependent hepatotoxicity and should be used with caution in patients with evidence of mild abnormalities in serum aminotransferase activity. The combination of naltrexone plus disulfiram should be avoided, since both drugs are potential hepatotoxins. Administration of naltrexone to patients who are physically dependent on opioids precipitates an acute withdrawal syndrome, so patients must be opioid-free before initiating naltrexone therapy. Naltrexone also blocks the therapeutic analgesic effects of usual doses of opioids.

Acamprosate

Acamprosate has been used in Europe for a number of years to treat alcohol dependence and was approved for this use by the FDA in 2004. Like ethanol, acamprosate has many molecular effects including actions on GABA, glutamate, serotonergic, noradrenergic, and dopaminergic receptors. Probably its best-characterized actions are as a weak NMDA-receptor antagonist and a $GABA_A$-receptor activator. In European clinical trials, acamprosate reduced short-term and long-term (more than 6 months) relapse rates when combined with psychotherapy. In a large American trial that compared acamprosate with naltrexone and with combined acamprosate and naltrexone therapy (the COMBINE study), acamprosate did not show a statistically significant effect alone or in combination with naltrexone.

Acamprosate is administered as 1–2 enteric-coated 333 mg tablets three times daily. It is poorly absorbed, and food reduces its absorption even further. Acamprosate is widely distributed and is eliminated renally. It does not appear to participate in drug-drug interactions. The most common adverse effects are gastrointestinal (nausea, vomiting, diarrhea) and rash. It should not be used in patients with severe renal impairment.

Disulfiram

Disulfiram causes extreme discomfort in patients who drink alcoholic beverages. Disulfiram alone has little effect; however, flushing, throbbing headache, nausea, vomiting, sweating, hypotension, and confusion occur within a few minutes after an individual taking disulfiram drinks alcohol. The effects may last 30 minutes in mild cases or several hours in severe ones. Disulfiram acts by inhibiting aldehyde dehydrogenase. Thus, alcohol is metabolized as usual, but acetaldehyde accumulates.

Disulfiram is rapidly and completely absorbed from the gastrointestinal tract; however, a period of 12 hours is required for its full action. Its elimination rate is slow, so that its action may persist for several days after the last dose. The drug inhibits the metabolism of many other therapeutic agents, including phenytoin, oral anticoagulants, and isoniazid. It should not be administered with medications that contain alcohol, including nonprescription medications such as those listed in Table 63–3. Disulfiram can cause small increases in liver function tests. Its safety in pregnancy has not been demonstrated.

Because adherence to disulfiram therapy is low and because the evidence from clinical trials for its effectiveness is weak, disulfiram is no longer commonly used.

Other Drugs

Several other drugs have shown efficacy in maintaining abstinence and reducing craving in chronic alcoholism, although none has FDA approval yet for this use. Such drugs include ondansetron, a serotonin 5-HT_3-receptor antagonist (see Chapters 16, 62); topiramate, a drug used for partial and generalized tonic-clonic seizures (see Chapter 24); and baclofen, a $GABA_B$ receptor antagonist used as a spasmolytic (see Chapter 27). Based on evidence from model systems, efforts are underway to explore agents that modulate cannabinoid CB1 receptors, corticotropin-releasing factor receptors, and GABA receptor systems, as well as several other possible targets. Rimonabant, a CB1 receptor antagonist, has been shown to suppress alcohol-related behaviors in animal models and is being tested in clinical trials of alcoholism.

■ PHARMACOLOGY OF OTHER ALCOHOLS

Other alcohols related to ethanol have wide applications as industrial solvents and occasionally cause severe poisoning. Of these, **methanol** and **ethylene glycol** are two of the most common causes of intoxication.

METHANOL

Methanol (methyl alcohol, wood alcohol) is widely used in the industrial production of synthetic organic compounds and as a constituent of many commercial solvents. In the home, methanol is most frequently found in the form of "canned heat" or in windshield-washing products. Poisonings occur from accidental ingestion of methanol-containing products or when it is misguidedly ingested as an ethanol substitute.

Methanol can be absorbed through the skin or from the respiratory or gastrointestinal tract and is then distributed in body water. The primary mechanism of elimination of methanol in humans is by oxidation to formaldehyde, formic acid, and CO_2 (Figure 23–3).

Animal species show great variability in mean lethal doses of methanol. The special susceptibility of humans to methanol toxicity is due to metabolism to formate and formaldehyde, not to methanol itself. Since the conversion of methanol to its toxic metabolites is relatively slow, there is often a delay of 6–30 hours before the appearance of severe toxicity.

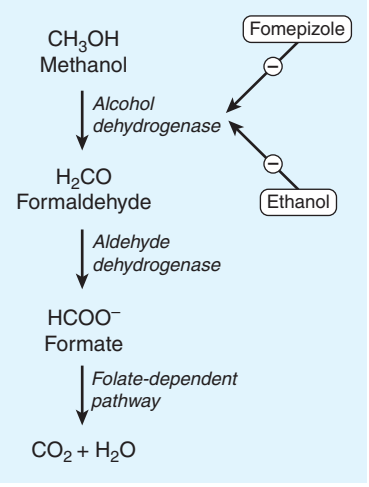

FIGURE 23–3 Methanol is converted to the toxic metabolites formaldehyde and formate by alcohol dehydrogenase and aldehyde dehydrogenase. By inhibiting alcohol dehydrogenase, fomepizole and ethanol reduce the formation of toxic metabolites.

Physical findings in early methanol poisoning are generally nonspecific, such as inebriation and gastritis, and possibly an elevated osmolar gap (see Chapter 58). In severe cases, the odor of formaldehyde may be present on the breath or in the urine. After a delay, the most characteristic symptom in methanol poisoning—visual disturbance—occurs along with anion gap metabolic acidosis. The visual disturbance is frequently described as "like being in a snowstorm" and can progress to blindness. Changes in the retina may sometimes be detected on examination, but these are usually late. The development of bradycardia, prolonged coma, seizures, and resistant acidosis all imply a poor prognosis. The cause of death in fatal cases is sudden cessation of respiration. A serum methanol concentration higher than 20 mg/dL warrants treatment, and a concentration higher than 50 mg/dL is considered serious enough to require hemodialysis. Serum formate levels are a better indication of clinical pathology but are not widely available.

The first treatment for methanol poisoning, as in all critical poisoning situations, is support of respiration. There are three specific modalities of treatment for severe methanol poisoning: suppression of metabolism by alcohol dehydrogenase to toxic products, hemodialysis to enhance removal of methanol and its toxic products, and alkalinization to counteract metabolic acidosis.

The enzyme chiefly responsible for methanol oxidation in the liver is alcohol dehydrogenase (Figure 23–3). **Fomepizole,** an alcohol dehydrogenase inhibitor, is approved for the treatment of methanol and ethylene glycol poisoning. It is administered intravenously in a loading dose of 15 mg/kg followed by 10 mg/kg every 12 hours for 48 hours and then 15 mg/kg every 12 hours thereafter until the serum methanol level falls below 20–30 mg/dL. The dosage increase after 48 hours is based on evidence that fomepizole rapidly induces its own metabolism by the cytochrome P450 system. Patients undergoing hemodialysis are given fomepizole more frequently (6 hours after the loading dose and every 4 hours thereafter). Fomepizole appears to be safe during the short time it is administered for treatment of methanol or ethylene glycol poisoning. The most common adverse effects are burning at the infusion site, headache, nausea, and dizziness. Intravenous ethanol is an alternative to fomepizole. It has a higher affinity than methanol for alcohol dehydrogenase; thus, saturation of the enzyme with ethanol reduces formate production. Ethanol is used intravenously as treatment for methanol and ethylene glycol poisoning. The dose-dependent characteristics of ethanol metabolism and the variability of ethanol metabolism require frequent monitoring of blood ethanol levels to ensure appropriate alcohol concentration.

In cases of severe poisoning, hemodialysis (discussed in Chapter 58) can be used to eliminate both methanol and formate from the blood. Two other measures are commonly taken. Because of profound metabolic acidosis in methanol poisoning, treatment with bicarbonate often is necessary. Since folate-dependent systems are responsible for the oxidation of formic acid to CO_2 in humans (Figure 23–3), folinic and folic acid are often administered to patients poisoned with methanol, although this has never been fully tested in clinical studies.

ETHYLENE GLYCOL

Polyhydric alcohols such as ethylene glycol (CH_2OHCH_2OH) are used as heat exchangers, in antifreeze formulations, and as industrial solvents. Young children and animals are sometimes attracted by the sweet taste of ethylene glycol and, rarely, it is ingested intentionally as an ethanol substitute or in attempted suicide. Although ethylene glycol itself is relatively harmless and eliminated by the kidney, it is metabolized to toxic aldehydes and oxalate.

Three stages of ethylene glycol overdose occur. Within the first few hours after ingestion, there is transient excitation followed by CNS depression. After a delay of 4–12 hours, severe metabolic acidosis develops from accumulation of acid metabolites and lactate. Finally, delayed renal insufficiency follows deposition of oxalate in renal tubules. The key to the diagnosis of ethylene glycol poisoning is recognition of anion gap acidosis, osmolar gap, and oxalate crystals in the urine in a patient without visual symptoms.

As with methanol poisoning, early fomepizole is the standard treatment for ethylene glycol poisoning. Intravenous treatment with fomepizole is initiated immediately, as described above for methanol poisoning, and continued until the patient's serum ethylene glycol concentration drops below a toxic threshold (20–30 mg/dL). Intravenous ethanol is an alternative to fomepizole in ethylene glycol poisoning. Hemodialysis effectively removes ethylene glycol and its toxic metabolites and is recommended for patients with a serum ethylene glycol concentration above 50 mg/dL, significant metabolic acidosis, and significant renal impairment. Fomepizole has reduced the need for hemodialysis, especially in patients with less severe acidosis and intact renal function.

SUMMARY The Alcohols and Associated Drugs

Subclass	Mechanism of Action	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
ALCOHOLS			
• Ethanol	Multiple effects on neurotransmitter receptors, ion channels, and signaling pathways	Antidote in methanol and ethylene glycol poisoning	Zero-order metabolism • duration depends on dose • *Toxicity:* Acutely, central nervous system depression and respiratory failure • chronically, damage to many systems, including liver, pancreas, gastrointestinal tract, and central and peripheral nervous systems • *Interactions:* Induces CYP2E1 • increased conversion of acetaminophen to toxic metabolite
• *Methanol: Poisonings result in toxic levels of formate, which causes characteristic visual disturbance plus coma, seizures, acidosis, and death due to respiratory failure*			
• *Ethylene glycol: Poisoning creates toxic aldehydes and oxalate, which causes kidney damage and severe acidosis*			
DRUGS USED IN ACUTE ETHANOL WITHDRAWAL			
• Benzodiazepines (eg, chlordiazepoxide, diazepam, lorazepam)	BDZ receptor agonists that facilitate GABA-mediated activation of $GABA_A$ receptors	Prevention and treatment of acute ethanol withdrawal syndrome	See Chapter 22
• Thiamine (vitamin B_1)	Essential vitamin required for synthesis of the coenzyme thiamine pyrophosphate	Administered to patients suspected of having alcoholism (those exhibiting acute alcohol intoxication or alcohol withdrawal syndrome) to prevent Wernicke-Korsakoff syndrome	Administered parenterally • *Toxicity:* None • *Interactions:* None
DRUGS USED IN CHRONIC ALCOHOLISM			
• Naltrexone	Nonselective competitive antagonist of opioid receptors	Reduced risk of relapse in individuals with alcoholism	Available as an oral or long-acting parenteral formulation • *Toxicity:* GI effects and liver toxicity; will precipitate a withdrawal reaction in individuals physically dependent on opioids and will prevent the analgesic effect of opioids
• Acamprosate	Poorly understood NMDA receptor antagonist and $GABA_A$ agonist effects	Reduced risk of relapse in individuals with alcoholism	*Toxicity:* GI effects and rash
• Disulfiram	Inhibits aldehyde dehydrogenase, resulting in aldehyde accumulation during ethanol ingestion	Deterrent to drinking in individuals with alcohol dependence	*Toxicity:* Little effect alone but severe and potentially dangerous flushing, headache, nausea, vomiting, and hypotension when combined with ethanol
DRUGS USED IN ACUTE METHANOL OR ETHYLENE GLYCOL TOXICITY			
• Fomepizole	Inhibits alcohol dehydrogenase, prevents conversion of methanol and ethylene glycol to toxic metabolites	Methanol and ethylene glycol poisoning	Orphan drug • *Toxicity:* Headache, nausea, dizziness, rare allergic reactions
• *Ethanol: Higher affinity than methanol or ethylene glycol for alcohol dehydrogenase; used to reduce metabolism of methanol and ethylene glycol to toxic products*			

PREPARATIONS AVAILABLE

DRUGS FOR THE TREATMENT OF ACUTE ALCOHOL WITHDRAWAL SYNDROME (see also Chapter 22 for other benzodiazepines)

Chlordiazepoxide HCl (generic, Librium)
Oral: 5, 10, 25 mg tablets

Diazepam (generic, Valium)
Oral: 2, 5, 10 mg tablets; 1, 5 mg/mL solutions
Rectal: 2.5, 10, 20 mg gel
Parenteral: 5 mg/mL for injection

Lorazepam (generic, Ativan)
Oral: 0.5, 1, 2 mg tablets; 2 mg/mL solution
Parenteral: 2, 4 mg/mL for injection

Oxazepam (generic)
Oral: 10, 15, 30 mg capsules

Thiamine HCl (generic)
Oral: 50, 100, 250, 500 mg tablets or capsules
Parenteral: 100 mg/mL for injection

DRUGS FOR THE PREVENTION OF ALCOHOL ABUSE

Acamprosate Calcium (Campral)
Oral: 333 mg delayed-release tablets

Disulfiram (Antabuse)
Oral: 250, 500 mg tablets

Naltrexone HCl (generic, ReVia)
Oral: 50 mg tablets
Parenteral (Vivitrol): 380 mg for IM injection once per month

DRUGS FOR THE TREATMENT OF ACUTE METHANOL OR ETHYLENE GLYCOL POISONING

Ethanol (generic)
Parenteral: 5% or 10% ethanol and 5% dextrose in water for IV infusion

Fomepizole (generic, Antizol)
Parenteral: 1 g/mL concentrate for IV injection

REFERENCES

Anton RF: Naltrexone for the management of alcohol dependence. N Engl J Med 2008;359:715.

Anton RF et al: Combined pharmacotherapies and behavioral interventions for alcohol dependence: The COMBINE study: A randomized controlled trial. JAMA 2006;295:2003.

Brent J: Fomepizole for ethylene glycol and methanol poisoning. N Engl J Med 2009;360:2216.

Brodie MS et al: Ethanol interactions with calcium-dependent potassium channels. Alcohol Clin Exp Res 2007;31:1625.

CDC Fetal Alcohol Syndrome Website: http://www.cdc.gov/ncbddd/fas/

Chen YC et al: Polymorphism of ethanol-metabolism genes and alcoholism: Correlation of allelic variations with the pharmacokinetic and pharmacodynamic consequences. Chem Biol Interact 2009;178:2.

Colombo G et al: The cannabinoid CB1 receptor antagonist, rimonabant, as a promising pharmacotherapy for alcohol dependence: Preclinical evidence. Mol Neurobiol 2007;36:102.

Crabbe JC et al: Alcohol-related genes: Contributions from studies with genetically engineered mice. Addict Biol 2006;11:195.

Das SK, Vasudevan DM: Alcohol-induced oxidative stress. Life Sci 2007; 81:177.

Edenberg HJ: The genetics of alcohol metabolism: Role of alcohol dehydrogenase and aldehyde dehydrogenase variants. Alcohol Res Health 2007; 30:5.

Heilig M, Egli M: Pharmacologic treatment of alcohol dependence: Target symptoms and target mechanisms. Pharmacol Ther 2006;111:855.

Johnson BA: Update on neuropharmacological treatments for alcoholism: Scientific basis and clinical findings. Biochem Pharmacol 2008;75:34.

Lepik KJ et al: Adverse drug events associated with the antidotes for methanol and ethylene glycol poisoning: A comparison of ethanol and fomepizole. Ann Emerg Med 2009;53:439.

Lieber CS: Medical disorders of alcoholism. N Engl J Med 1995;333:1058.

Lobo IA, Harris RA: GABA(A) receptors and alcohol. Pharmacol Biochem Behav 2008;90:90.

Mayfield RD, Harris RA, Schuckit MA: Genetic factors influencing alcohol dependence. Br J Pharmacol 2008;154:275.

McIntire SL: Ethanol. WormBook 2010;29:1.

National Institute on Alcohol Abuse and Alcoholism Website: http://www.niaaa.nih.gov/

Olson KR et al (editors): *Poisoning and Drug Overdose,* 5th ed. McGraw-Hill, 2006.

Shuckit MA: Alcohol-use disorders. Lancet 2009;373:492.

Shuckit MA: *Drug and Alcohol Abuse: A Clinical Guide to Diagnosis and Treatment,* 6th ed. Springer, 2006.

Srisurapanont M, Jarusuraisin N: Opioid antagonists for alcohol dependence. Cochrane Database Syst Rev 2005;(1):CD001867.

Tetrault JM, O'Connor PG: Substance abuse and withdrawal in the critical care setting. Crit Care Clin 2008;24:767.

Wolf FW, Heberlein U: Invertebrate models of drug abuse. J Neurobiol 2003;54:161.

You M, Crabb DW: Recent advances in alcoholic liver disease II. Minireview: Molecular mechanisms of alcoholic fatty liver. Am J Physiol Gastrointest Liver Physiol 2004;287:G1.

CASE STUDY ANSWER

This young man exhibits classic signs and symptoms of acute alcohol poisoning, which is confirmed by the blood alcohol concentration. We do not know from the case whether the patient was tolerant to the effects of alcohol but note that his blood alcohol concentration was in the lethal range for a nontolerant individual. Death most likely resulted from respiratory and cardiovascular collapse prior to medical treatment, complicated by a chemical pneumonitis secondary to aspiration of vomitus. The treatment of acute alcohol poisoning includes standard supportive care of airway, breathing, and circulation (see Chapter 58). Intravenous access would be obtained and used to administer dextrose and thiamine, as well as other electrolytes and vitamins. If a young, previously healthy individual receives medical care in time, supportive care will most likely be highly effective. As the patient recovers, it is important to be vigilant for signs and symptoms of the alcohol withdrawal syndrome.

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CHAPTER 24

Antiseizure Drugs

Roger J. Porter, MD, &
Brian S. Meldrum, MB, PhD

CASE STUDY*

A 23-year-old woman presents to the office for consultation regarding her antiseizure medications. Seven years ago, this otherwise healthy young woman had a generalized tonic-clonic seizure (GTCS) at home. She was rushed to the emergency department, at which time she was alert but complained of headache. A consulting neurologist placed her on levetiracetam, 500 mg bid. Four days later, EEG showed rare right temporal sharp waves. MRI was normal. One year after this episode, a repeat EEG was unchanged, and levetiracetam was gradually increased to 1000 mg bid. The patient had no significant adverse effects from this dosage. At age 21, she had a second GTCS while in college; further discussion with her roommate at that time revealed a history of two recent episodes of 1–2 minutes of altered consciousness with lip smacking (complex partial seizures). A repeat EEG showed occasional right temporal spikes. Lamotrigine was gradually added to the regimen to a dosage of 200 mg bid. Since then, the patient has been seizure-free for almost 2 years but now comes to the office for a medication review. Gradual discontinuation of levetiracetam is planned if the patient continues to do well for another year, although risk of recurrent seizures is always present when medications are withdrawn.

Approximately 1% of the world's population has epilepsy, the second most common neurologic disorder after stroke. Although standard therapy permits control of seizures in 80% of these patients, millions (500,000 people in the USA alone) have uncontrolled epilepsy. Epilepsy is a heterogeneous symptom complex—a chronic disorder characterized by recurrent seizures. Seizures are finite episodes of brain dysfunction resulting from abnormal discharge of cerebral neurons. The causes of seizures are many and include the full range of neurologic diseases—from infection to neoplasm and head injury. In some subgroups, heredity has proved to be a predominant factor. Single gene defects, usually of an autosomal dominant nature involving genes coding voltage-gated ion channels or $GABA_A$ receptors, have been shown to account for a small number of familial generalized epilepsies. Commonly, one family shows multiple epilepsy syndromes including, for example, febrile seizures, absence attacks, and juvenile myoclonic epilepsy.

The antiseizure drugs described in this chapter are also used in patients with febrile seizures or with seizures occurring as part of an acute illness such as meningitis. The term "epilepsy" is not usually applied to such patients unless chronic seizures develop later. Seizures are occasionally caused by an acute underlying toxic or metabolic disorder, in which case appropriate therapy should be directed toward the specific abnormality, eg, hypocalcemia. In most cases of epilepsy, however, the choice of medication depends on the empiric seizure classification.

Drug Development for Epilepsy

For a long time it was assumed that a single **antiepileptic drug (AED)** could be developed for the treatment of all forms of epilepsy. However, the causes of epilepsy are extremely diverse, encompassing genetic and developmental defects and infective, traumatic, neoplastic, and degenerative disease processes. Drug therapy to date shows little evidence of etiologic specificity. There is some specificity according to seizure type (Table 24–1), which is most clearly seen with generalized seizures of the absence type. These are typically seen with 2–3 Hz spike-and-wave

*This case description includes the answers to implied questions regarding therapy.

TABLE 24–1 Classification of seizure types.

Partial seizures
Simple partial seizures
Complex partial seizures
Partial seizures secondarily generalized
Generalized seizures
Generalized tonic-clonic (grand mal) seizures
Absence (petit mal) seizures
Tonic seizures
Atonic seizures
Clonic and myoclonic seizures
Infantile spasms[1]

[1]An epileptic syndrome rather than a specific seizure type; drugs useful in infantile spasms will be reviewed separately.

discharges on the electroencephalogram, which respond to ethosuximide and valproate but can be exacerbated by phenytoin and carbamazepine. Drugs acting selectively on absence seizures can be identified by animal screens, using either threshold pentylenetetrazol clonic seizures in mice or rats or mutant mice showing absence-like episodes (so-called lethargic, star-gazer, or tottering mutants). In contrast, the **maximal electroshock (MES)** test, with suppression of the tonic extensor phase, identifies drugs such as phenytoin, carbamazepine, and lamotrigine, which are active against generalized tonic-clonic seizures and complex partial seizures. The maximal electroshock test as the major initial screen for new drugs has led predominantly to the identification of drugs with a mechanism of action involving prolonged inactivation of the voltage-gated Na^+ channel. Limbic seizures induced in rats by the process of electrical kindling (involving repeated episodes of focal electrical stimulation) probably provide a better screen for predicting efficacy in complex partial seizures.

Existing antiseizure drugs provide adequate seizure control in about two thirds of patients. So-called "drug resistance" may be observed from the onset of attempted therapy or may develop after a period of relatively successful therapy. Explanations are being sought in terms of impaired access of the drugs to target sites or insensitivity of target molecules to them. In children, some severe seizure syndromes associated with progressive brain damage are very difficult to treat. In adults, some focal seizures are refractory to medications. Some, particularly in the temporal lobe, are amenable to surgical resection. Some of the drug-resistant population may respond to **vagus nerve stimulation (VNS),** a nonpharmacologic treatment for epilepsy now widely approved for treatment of patients with partial seizures. VNS is indicated for refractory cases or for patients in whom antiseizure drugs are poorly tolerated. Stimulating electrodes are implanted on the left vagus nerve, and the pacemaker is implanted in the chest wall or axilla. Use of this device may permit seizure control with lower doses of drugs. Other devices, using various paradigms of electrical stimulation, are in clinical development.

New antiseizure drugs are being sought not only by the screening tests noted above but also by more focused approaches. Compounds are sought that act by one of three mechanisms: (1) enhancement of GABAergic (inhibitory) transmission, (2) diminution of excitatory (usually glutamatergic) transmission, or (3) modification of ionic conductances. Presynaptic effects on transmitter release appear particularly important, and some molecular targets are known, eg, SV_2A (see below).

Although it is widely recognized that current antiseizure drugs are palliative rather than curative, successful strategies for identifying drugs that are either disease modifying or that prevent epileptogenesis have proved elusive. Neuronal targets for current and potential antiseizure drugs include both excitatory and inhibitory synapses. Figure 24–1 represents a glutamatergic (excitatory) synapse, and Figure 24–2 indicates targets in a GABAergic (inhibitory) synapse.

BASIC PHARMACOLOGY OF ANTISEIZURE DRUGS

Chemistry

Until 1990, approximately 16 antiseizure drugs were available, and 13 of them can be classified into five very similar chemical groups: barbiturates, hydantoins, oxazolidinediones, succinimides, and acetylureas. These groups have in common a similar heterocyclic ring structure with a variety of substituents (Figure 24–3). For drugs with this basic structure, the substituents on the heterocyclic ring determine the pharmacologic class, either anti-MES or antipentylenetetrazol. Very small changes in structure can dramatically alter the mechanism of action and clinical properties of the compound. The remaining drugs in this older group—carbamazepine, valproic acid, and the benzodiazepines—are structurally dissimilar, as are the newer compounds marketed since 1990, ie, eslicarbazepine, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, retigabine, rufinamide, stiripentol, tiagabine, topiramate, vigabatrin, and zonisamide.

Pharmacokinetics

The antiseizure drugs exhibit many similar pharmacokinetic properties—even those whose structural and chemical properties are quite diverse—because most have been selected for oral activity and all must enter the central nervous system. Although many of these compounds are only slightly soluble, absorption is usually good, with 80–100% of the dose reaching the circulation. Most antiseizure drugs (other than phenytoin, tiagabine, and valproic acid) are not highly bound to plasma proteins.

Antiseizure drugs are cleared chiefly by hepatic mechanisms, although they have low extraction ratios (see Chapter 3). Many are converted to active metabolites that are also cleared by the

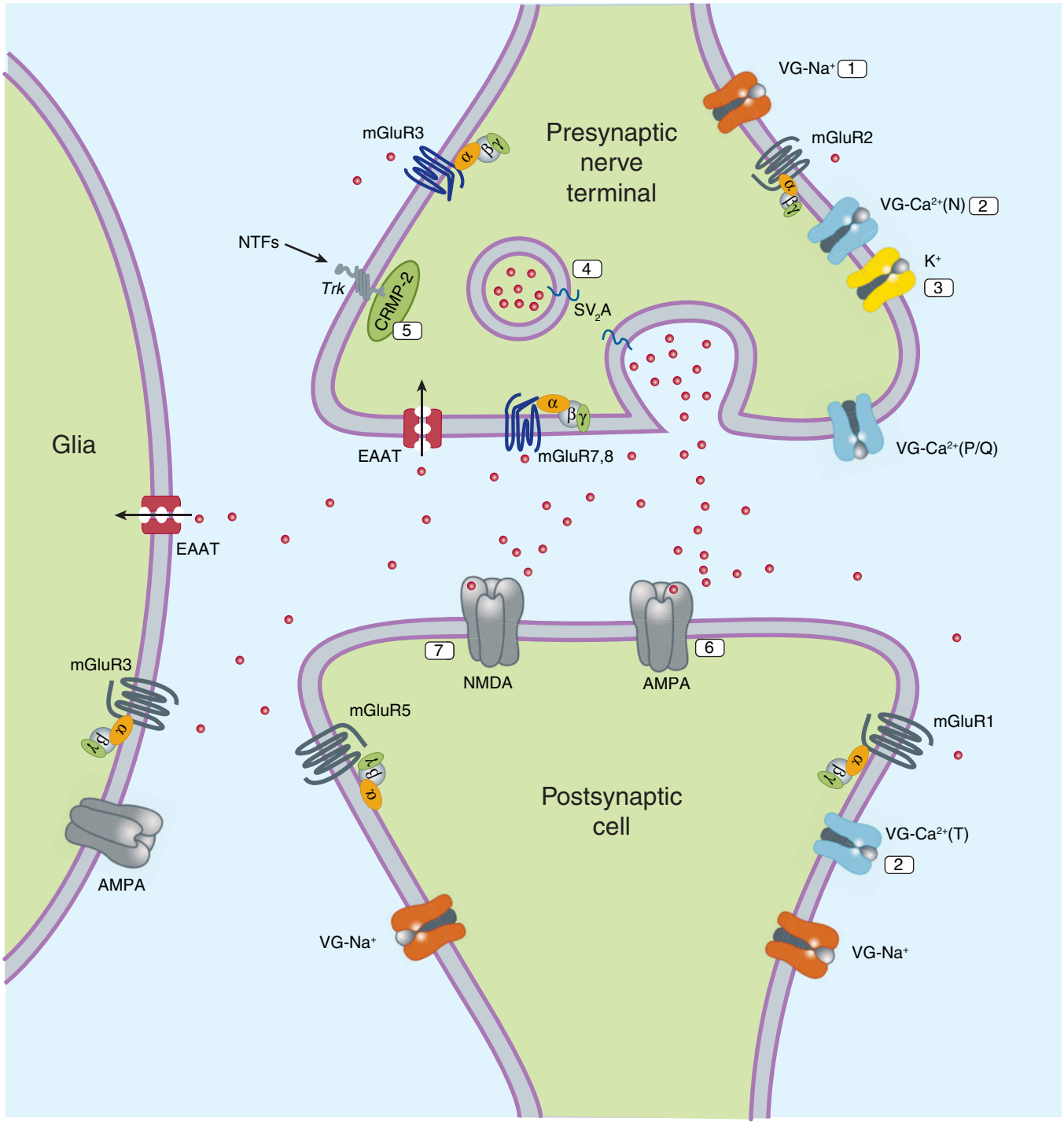


FIGURE 24–1 Molecular targets for antiseizure drugs at the excitatory, glutamatergic synapse. Presynaptic targets diminishing glutamate release include 1, voltage-gated (VG) Na^+ channels (phenytoin, carbamazepine, lamotrigine, and lacosamide); 2, VG-Ca^{2+} channels (ethosuximide, lamotrigine, gabapentin, and pregabalin); 3, K^+ channels (retigabine); synaptic vesicle proteins, 4, SV_2A (levetiracetam); and 5, CRMP-2, collapsin-response mediator protein-2 (lacosamide). Postsynaptic targets include 6, AMPA receptors (blocked by phenobarbital, topiramate, and lamotrigine) and 7, NMDA receptors (blocked by felbamate). EAAT, excitatory amino acid transporter. Red dots represent glutamate.

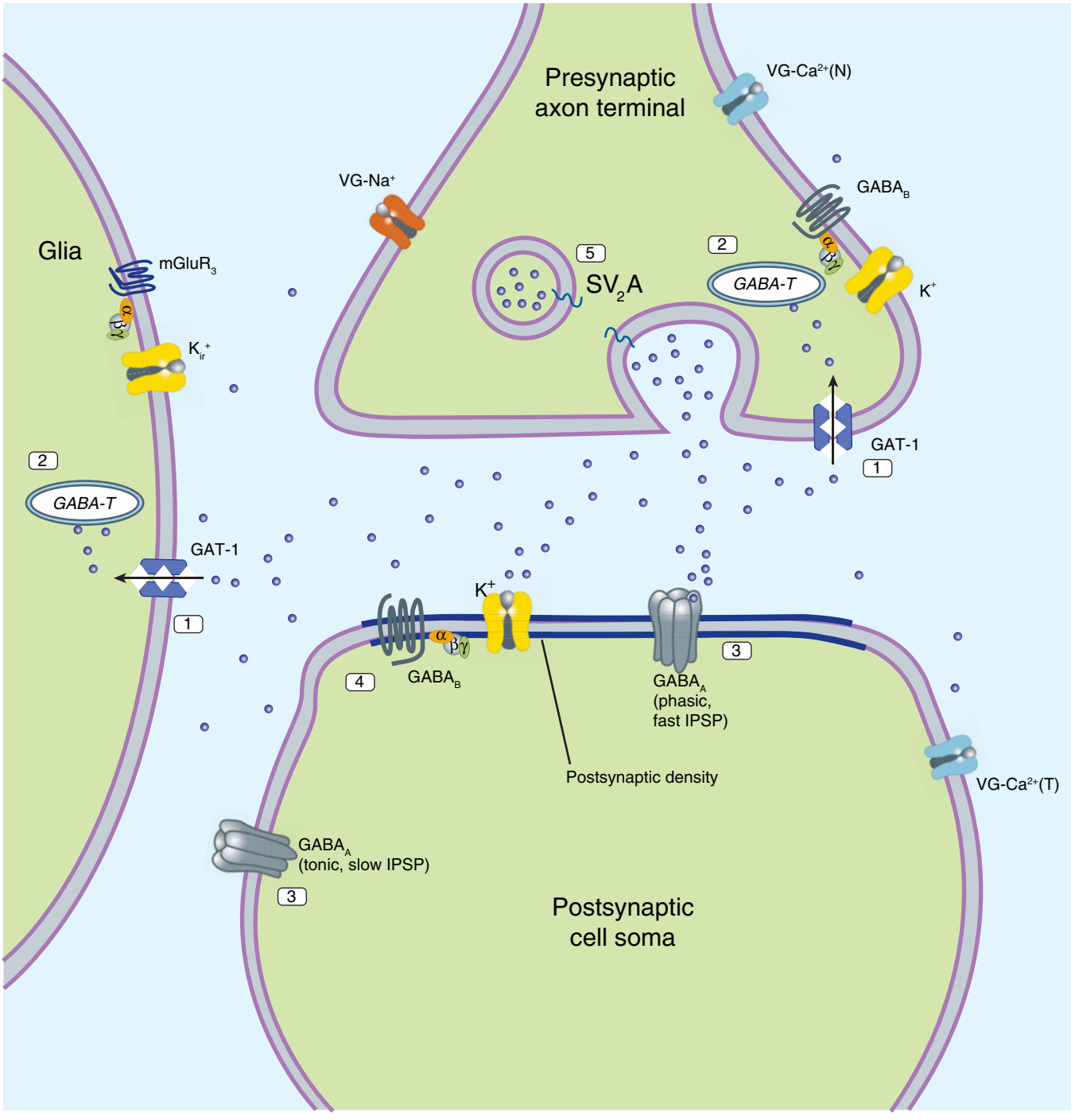


FIGURE 24–2 Molecular targets for antiseizure drugs at the inhibitory, GABAergic synapse. These include "specific" targets: 1, GABA transporters (especially GAT-1, tiagabine); 2, GABA-transaminase (GABA-T, vigabatrin); 3, $GABA_A$ receptors (benzodiazepines); potentially, 4, $GABA_B$ receptors; and 5, synaptic vesicular proteins (SVA_2). Effects may also be mediated by "nonspecific" targets such as by voltage-gated (VG) ion channels and synaptic proteins. IPSP, inhibitory postsynaptic potential. Blue dots represent GABA.

liver. These drugs are predominantly distributed into total body water. Plasma clearance is relatively slow; many antiseizure drugs are therefore considered to be medium to long acting. Some have half-lives longer than 12 hours. Many of the older antiseizure drugs are potent inducers of hepatic microsomal enzyme activity. Compliance is better with less frequent administration; thus extended-release formulations permitting once- or twice-daily administration may offer an advantage.

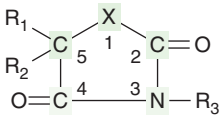


FIGURE 24–3 Antiseizure heterocyclic ring structure. The X varies as follows: hydantoin derivatives, –N–; barbiturates, –C–N–; oxazolidinediones, –O–; succinimides, –C–; acetylureas, $–NH_2$ (N connected to C_2). R_1, R_2, and R_3 vary within each subgroup.

DRUGS USED IN PARTIAL SEIZURES & GENERALIZED TONIC-CLONIC SEIZURES

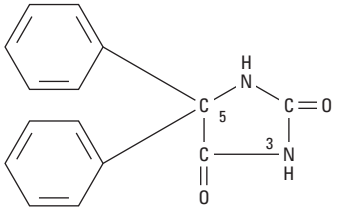
The classic major drugs for partial and generalized tonic-clonic seizures are phenytoin (and congeners), carbamazepine, valproate, and the barbiturates. However, the availability of newer drugs—eslicarbazepine, lamotrigine, levetiracetam, gabapentin, oxcarbazepine, pregabalin, retigabine, topiramate, vigabatrin, lacosamide, and zonisamide—is altering clinical practice in countries where these compounds are available. The next section of the chapter is a description of major drugs from a historical and structural perspective. Factors involved in the clinical choice of drugs are described in the last section of the chapter.

PHENYTOIN

Phenytoin is the oldest nonsedative antiseizure drug, introduced in 1938 after a systematic evaluation of compounds such as phenobarbital that altered electrically induced seizures in laboratory animals. It was known for decades as **diphenylhydantoin.**

Chemistry

Phenytoin is a diphenyl-substituted hydantoin with the structure shown. It has much lower sedative properties than compounds with alkyl substituents at the 5 position. A more soluble prodrug of phenytoin, **fosphenytoin,** is available for parenteral use; this phosphate ester compound is rapidly converted to phenytoin in the plasma.



Phenytoin

Mechanism of Action

Phenytoin has major effects on several physiologic systems. It alters Na^+, K^+, and Ca^{2+} conductance, membrane potentials, and the concentrations of amino acids and the neurotransmitters norepinephrine, acetylcholine, and γ-aminobutyric acid (GABA). Studies with neurons in cell culture show that phenytoin blocks sustained high-frequency repetitive firing of action potentials (Figure 24–4). This effect is seen at therapeutically relevant concentrations. It is a use-dependent effect (see Chapter 14) on Na^+ conductance, arising from preferential binding to—and prolongation of—the inactivated state of the Na^+ channel. This effect is also seen with therapeutically relevant concentrations of carbamazepine, lamotrigine, and valproate and probably contributes to their antiseizure action in the electroshock model and in partial seizures. Phenytoin also blocks the persistent Na^+ current, as do several other AEDs including valproate, topiramate, and ethosuximide.

In addition, phenytoin paradoxically causes excitation in some cerebral neurons. A reduction of calcium permeability, with inhibition of calcium influx across the cell membrane, may explain the ability of phenytoin to inhibit a variety of calcium-induced secretory processes, including release of hormones and neurotransmitters. Recording of excitatory and inhibitory postsynaptic potentials show that phenytoin decreases the synaptic release of glutamate

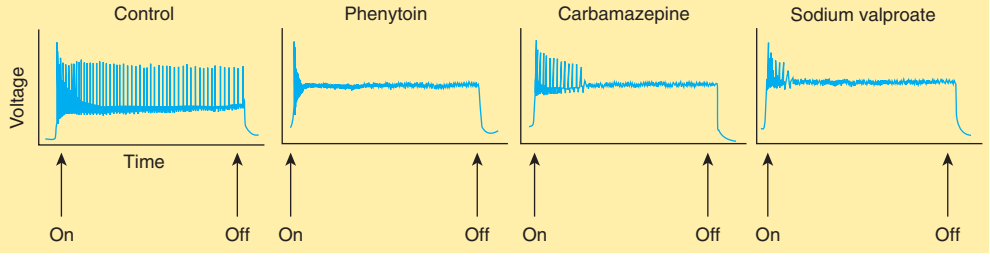


FIGURE 24–4 Effects of three antiseizure drugs on sustained high-frequency firing of action potentials by cultured neurons. Intracellular recordings were made from neurons while depolarizing current pulses, approximately 0.75 s in duration, were applied (on-off step changes indicated by arrows). In the absence of drug, a series of high-frequency repetitive action potentials filled the entire duration of the current pulse. Phenytoin, carbamazepine, and sodium valproate all markedly reduced the number of action potentials elicited by the current pulses. (Modified and reproduced, with permission, from Macdonald RL, Meldrum BS: Principles of anti-epileptic drug action. In: Levy RH et al [editors]: *Antiepileptic Drugs,* 4th ed. Raven Press, 1995.)

and enhances the release of GABA. The mechanism of phenytoin's action probably involves a combination of actions at several levels. At therapeutic concentrations, the major action of phenytoin is to block Na^+ channels and inhibit the generation of rapidly repetitive action potentials. Presynaptic actions on glutamate and GABA release probably arise from actions other than those on voltage-gated Na^+ channels.

Clinical Uses

Phenytoin is effective against partial seizures and generalized tonic-clonic seizures. In the latter, it appears to be effective against attacks that are either primary or secondary to another seizure type.

Pharmacokinetics

Absorption of phenytoin is highly dependent on the formulation of the dosage form. Particle size and pharmaceutical additives affect both the rate and the extent of absorption. Absorption of phenytoin sodium from the gastrointestinal tract is nearly complete in most patients, although the time to peak may range from 3 to 12 hours. Absorption after intramuscular injection is unpredictable, and some drug precipitation in the muscle occurs; this route of administration is not recommended for phenytoin. In contrast, fosphenytoin, a more soluble phosphate prodrug of phenytoin, is well absorbed after intramuscular administration.

Phenytoin is highly bound to plasma proteins. The total plasma level decreases when the percentage that is bound decreases, as in uremia or hypoalbuminemia, but correlation of free levels with clinical states remains uncertain. Drug concentration in cerebrospinal fluid is proportionate to the free plasma level. Phenytoin accumulates in brain, liver, muscle, and fat.

Phenytoin is metabolized to inactive metabolites that are excreted in the urine. Only a very small proportion of the dose is excreted unchanged.

The elimination of phenytoin is dose-dependent. At very low blood levels, phenytoin metabolism follows first-order kinetics. However, as blood levels rise within the therapeutic range, the maximum capacity of the liver to metabolize phenytoin is approached. Further increases in dosage, though relatively small, may produce very large changes in phenytoin concentrations (Figure 24–5). In such cases, the half-life of the drug increases markedly, steady state is not achieved in routine fashion (since the plasma level continues to rise), and patients quickly develop symptoms of toxicity.

The half-life of phenytoin varies from 12 to 36 hours, with an average of 24 hours for most patients in the low to mid therapeutic range. Much longer half-lives are observed at higher concentrations. At low blood levels, it takes 5–7 days to reach steady-state blood levels after every dosage change; at higher levels, it may be 4–6 weeks before blood levels are stable.

Therapeutic Levels & Dosage

The therapeutic plasma level of phenytoin for most patients is between 10 and 20 mcg/mL. A loading dose can be given either orally or intravenously; the latter, using fosphenytoin, is the method of choice for convulsive status epilepticus (discussed later). When oral therapy is started, it is common to begin adults at a dosage of 300 mg/d, regardless of body weight. This may be acceptable in some patients, but it frequently yields steady-state blood levels below 10 mcg/mL, which is the minimum therapeutic level for most patients. If seizures continue, higher doses are usually necessary to achieve plasma levels in the upper therapeutic range. Because of its dose-dependent kinetics, some toxicity may occur with only small increments in dosage. The phenytoin dosage should be increased each time by only 25–30 mg in adults, and ample time should be allowed for the new steady state to be achieved before further increasing the dosage. A common clinical error is to increase the dosage directly from 300 mg/d to 400 mg/d; toxicity frequently occurs at a variable time thereafter. In children, a dosage of 5 mg/kg/d should be followed by readjustment after steady-state plasma levels are obtained.

Two types of oral phenytoin sodium are currently available in the USA, differing in their respective rates of dissolution; one is absorbed rapidly and one more slowly. Only the slow-release extended-action formulation can be given in a single daily dosage, and care must be used when changing brands (see Preparations Available). Although a few patients being given phenytoin on a long-term basis have been proved to have low blood levels from poor absorption or rapid metabolism, the most common cause of low levels is poor compliance. Fosphenytoin sodium is available for intravenous or intramuscular use and replaces intravenous phenytoin sodium, a much less soluble form of the drug.

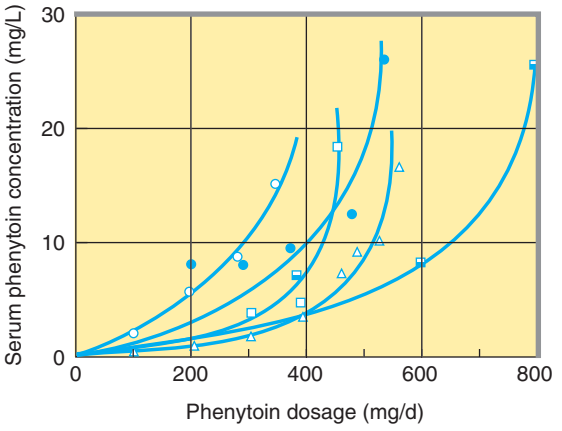


FIGURE 24–5 Nonlinear relationship of phenytoin dosage and plasma concentrations. Five patients (identified by different symbols) received increasing dosages of phenytoin by mouth, and the steady-state serum concentration was measured at each dosage. The curves are not linear, since, as the dosage increases, the metabolism is saturable. Note also the marked variation among patients in the serum levels achieved at any dosage. (Modified, with permission, from Jusko WJ: Bioavailability and disposition kinetics of phenytoin in man. In: Kellaway P, Peterson I [editors]: *Quantitative Analytic Studies in Epilepsy.* Raven Press, 1977.)

Drug Interactions & Interference with Laboratory Tests

Drug interactions involving phenytoin are primarily related to protein binding or to metabolism. Since phenytoin is 90% bound to plasma proteins, other highly bound drugs, such as phenylbutazone and sulfonamides, can displace phenytoin from its binding site. In theory, such displacement may cause a transient increase in free drug. A decrease in protein binding—eg, from hypoalbuminemia—results in a decrease in the total plasma concentration of drug but not the free concentration. Intoxication may occur if efforts are made to maintain total drug levels in the therapeutic range by increasing the dose. The protein binding of phenytoin is decreased in the presence of renal disease. The drug has an affinity for thyroid-binding globulin, which confuses some tests of thyroid function; the most reliable screening test of thyroid function in patients taking phenytoin appears to be measurement of thyroid-stimulating hormone (TSH).

Phenytoin has been shown to induce microsomal enzymes responsible for the metabolism of a number of drugs. Autostimulation of its own metabolism, however, appears to be insignificant.

Toxicity

Dose-related adverse effects caused by phenytoin are often similar to those caused by other antiseizure drugs in this group, making differentiation difficult in patients receiving multiple drugs. Nystagmus occurs early, as does loss of smooth extraocular pursuit movements, but neither is an indication for decreasing the dose. Diplopia and ataxia are the most common dose-related adverse effects requiring dosage adjustment; sedation usually occurs only at considerably higher levels. Gingival hyperplasia and hirsutism occur to some degree in most patients; the latter can be especially unpleasant in women. Long-term use is associated in some patients with coarsening of facial features and with mild peripheral neuropathy, usually manifested by diminished deep tendon reflexes in the lower extremities. Long-term use may also result in abnormalities of vitamin D metabolism, leading to osteomalacia. Low folate levels and megaloblastic anemia have been reported, but the clinical importance of these observations is unknown.

Idiosyncratic reactions to phenytoin are relatively rare. A skin rash may indicate hypersensitivity of the patient to the drug. Fever may also occur, and in rare cases the skin lesions may be severe and exfoliative. Lymphadenopathy may be difficult to distinguish from malignant lymphoma, and although some studies suggest a causal relationship between phenytoin and Hodgkin's disease, the data are far from conclusive. Hematologic complications are exceedingly rare, although agranulocytosis has been reported in combination with fever and rash.

MEPHENYTOIN, ETHOTOIN, & PHENACEMIDE

Many congeners of phenytoin have been synthesized, but only three have been marketed in the USA, and one of these (phenacemide) has been withdrawn. The other two congeners, mephenytoin and ethotoin, like phenytoin, appear to be most effective against generalized tonic-clonic seizures and partial seizures. No well-controlled clinical trials have documented their effectiveness. The incidence of severe reactions such as dermatitis, agranulocytosis, or hepatitis is higher for mephenytoin than for phenytoin.

Ethotoin may be recommended for patients who are hypersensitive to phenytoin, but larger doses are required. The adverse effects and toxicity are generally less severe than those associated with phenytoin, but the drug appears to be less effective.

Both ethotoin and mephenytoin share with phenytoin the property of saturable metabolism within the therapeutic dosage range. Careful monitoring of the patient during dosage alterations with either drug is essential. Mephenytoin is metabolized to 5,5-ethylphenylhydantoin via demethylation. This metabolite, **nirvanol,** contributes most of the antiseizure activity of mephenytoin. Both mephenytoin and nirvanol are hydroxylated and undergo subsequent conjugation and excretion. Therapeutic levels for mephenytoin range from 5 to 16 mcg/mL, and levels above 20 mcg/mL are considered toxic.

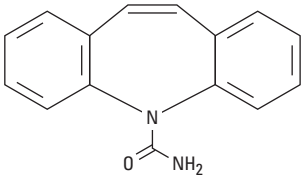
Therapeutic blood levels of nirvanol are between 25 and 40 mcg/mL. A therapeutic range for ethotoin has not been established.

CARBAMAZEPINE

Closely related to imipramine and other antidepressants, carbamazepine is a tricyclic compound effective in treatment of bipolar depression. It was initially marketed for the treatment of trigeminal neuralgia but has proved useful for epilepsy as well.

Chemistry

Although not obvious from a two-dimensional representation of its structure, carbamazepine has many similarities to phenytoin. The ureide moiety (–N–CO–NH_2) in the heterocyclic ring of most antiseizure drugs is also present in carbamazepine. Three-dimensional structural studies indicate that its spatial conformation is similar to that of phenytoin.



Carbamazepine

Mechanism of Action

The mechanism of action of carbamazepine appears to be similar to that of phenytoin. Like phenytoin, carbamazepine shows activity against maximal electroshock seizures. Carbamazepine, like phenytoin, blocks Na^+ channels at therapeutic concentrations and

inhibits high-frequency repetitive firing in neurons in culture (Figure 24–4). It also acts presynaptically to decrease synaptic transmission. Potentiation of a voltage-gated K^+ current has also been described. These effects probably account for the anticonvulsant action of carbamazepine. Binding studies show that carbamazepine interacts with adenosine receptors, but the functional significance of this observation is not known.

Clinical Uses

Although carbamazepine has long been considered a drug of choice for both partial seizures and generalized tonic-clonic seizures, some of the newer antiseizure drugs are beginning to displace it from this role. Carbamazepine is not sedative in its usual therapeutic range. The drug is also very effective in some patients with trigeminal neuralgia, although older patients may tolerate higher doses poorly, with ataxia and unsteadiness. Carbamazepine is also useful for controlling mania in some patients with bipolar disorder.

Pharmacokinetics

The rate of absorption of carbamazepine varies widely among patients, although almost complete absorption apparently occurs in all. Peak levels are usually achieved 6–8 hours after administration. Slowing absorption by giving the drug after meals helps the patient tolerate larger total daily doses.

Distribution is slow, and the volume of distribution is roughly 1 L/kg. The drug is approximately 70% bound to plasma proteins; no displacement of other drugs from protein binding sites has been observed.

Carbamazepine has a very low systemic clearance of approximately 1 L/kg/d at the start of therapy. The drug has a notable ability to induce microsomal enzymes. Typically, the half-life of 36 hours observed in subjects after an initial single dose decreases to as little as 8–12 hours in subjects receiving continuous therapy. Considerable dosage adjustments are thus to be expected during the first weeks of therapy. Carbamazepine also alters the clearance of other drugs (see below).

Carbamazepine is completely metabolized in humans to several derivatives. One of these, carbamazepine-10,11-epoxide, has been shown to have anticonvulsant activity. The contribution of this and other metabolites to the clinical activity of carbamazepine is unknown.

Therapeutic Levels & Dosage

Carbamazepine is available only in oral form. The drug is effective in children, in whom a dosage of 15–25 mg/kg/d is appropriate. In adults, daily doses of 1 g or even 2 g are tolerated. Higher dosage is achieved by giving multiple divided doses daily. Extended-release preparations permit twice-daily dosing for most patients. In patients in whom the blood is drawn just before the morning dose (trough level), the therapeutic level is usually 4–8 mcg/mL. Although many patients complain of diplopia at drug levels above 7 mcg/mL, others can tolerate levels above 10 mcg/mL, especially with monotherapy. Extended-release formulations that overcome some of these issues are now available.

Drug Interactions

Drug interactions involving carbamazepine are almost exclusively related to the drug's enzyme-inducing properties. As noted previously, the increased metabolic capacity of the hepatic enzymes may cause a reduction in steady-state carbamazepine concentrations and an increased rate of metabolism of other drugs, eg, primidone, phenytoin, ethosuximide, valproic acid, and clonazepam. Other drugs such as valproic acid may inhibit carbamazepine clearance and increase steady-state carbamazepine blood levels. Other anticonvulsants, however, such as phenytoin and phenobarbital, may decrease steady-state concentrations of carbamazepine through enzyme induction. No clinically significant protein-binding interactions have been reported.

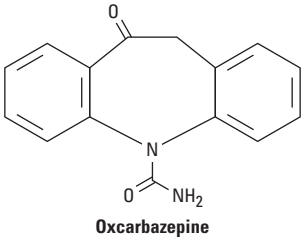
Toxicity

The most common dose-related adverse effects of carbamazepine are diplopia and ataxia. The diplopia often occurs first and may last less than an hour during a particular time of day. Rearrangement of the divided daily dose can often remedy this complaint. Other dose-related complaints include mild gastrointestinal upsets, unsteadiness, and, at much higher doses, drowsiness. Hyponatremia and water intoxication have occasionally occurred and may be dose related.

Considerable concern exists regarding the occurrence of idiosyncratic blood dyscrasias with carbamazepine, including fatal cases of aplastic anemia and agranulocytosis. Most of these have been in elderly patients with trigeminal neuralgia, and most have occurred within the first 4 months of treatment. The mild and persistent leukopenia seen in some patients is not necessarily an indication to stop treatment but requires careful monitoring. The most common idiosyncratic reaction is an erythematous skin rash; other responses such as hepatic dysfunction are unusual.

OXCARBAZEPINE

Oxcarbazepine is closely related to carbamazepine and is useful in the same seizure types, but it may have an improved toxicity profile. Oxcarbazepine has a half-life of only 1–2 hours. Its activity, therefore, resides almost exclusively in the 10-hydroxy metabolite (especially the *S*(+) enantiomer, eslicarbazepine), to which it is rapidly converted and which has a half-life similar to that of carbamazepine, ie, 8–12 hours. The drug is mostly excreted as the glucuronide of the 10-hydroxy metabolite.



Oxcarbazepine

Oxcarbazepine is less potent than carbamazepine, both in animal models of epilepsy and in epileptic patients; clinical doses of oxcarbazepine may need to be 50% higher than those of carbamazepine to obtain equivalent seizure control. Some studies report fewer hypersensitivity reactions to oxcarbazepine, and cross-reactivity with carbamazepine does not always occur. Furthermore, the drug appears to induce hepatic enzymes to a lesser extent than carbamazepine, minimizing drug interactions. Although hyponatremia may occur more commonly with oxcarbazepine than with carbamazepine, most adverse effects that occur with oxcarbazepine are similar in character to reactions reported with carbamazepine.

ESLICARBAZINE

Eslicarbazepine acetate (ESL) is a prodrug that has been approved in Europe as adjunctive therapy in adults with partial-onset seizures, with or without secondary generalization. ESL is more rapidly converted to *S*(+)-licarbazine (eslicarbazine) than is oxcarbazepine; clearly both prodrugs have the same metabolite as active product. The mechanism of action of carbamazepine, oxcarbazepine, and ESL appears to be the same, ie, blocking of voltage-gated Na^+ channels. The *R*(–) enantiomer has some activity, but much less than its counterpart.

Clinically, the drug is similar to carbamazepine and oxcarbazepine in its spectrum of action, but it is less well studied in other possible indications. The possible advantage of ESL is its once-daily dosing regimen. The measured half-life of the *S*(+) enantiomer is 9–11 hours. The drug is administered at a dosage of 400–1200 mg/d; titration is typically required for the higher doses.

Minimal drug level effects are observed with coadministration of carbamazepine, levetiracetam, lamotrigine, topiramate, and valproate. Oral contraceptives may be less effective with concomitant ESL administration.

PHENOBARBITAL

Aside from the bromides, phenobarbital is the oldest of the currently available antiseizure drugs. Although it has long been considered one of the safest of the antiseizure agents, the use of other medications with lesser sedative effects has been urged. Many consider the barbiturates the drugs of choice for seizures only in infants.

Chemistry

The four derivatives of barbituric acid clinically useful as antiseizure drugs are phenobarbital, mephobarbital, metharbital, and primidone. The first three are so similar that they are considered together. Metharbital is methylated barbital, and mephobarbital is methylated phenobarbital; both are demethylated in vivo. The pK_as of these three weak acid compounds range from 7.3 to 7.9. Slight changes in the normal acid-base balance, therefore, can cause significant fluctuation in the ratio of the ionized to the nonionized species. This is particularly important for phenobarbital, the most commonly used barbiturate, whose pK_a is similar to the plasma pH of 7.4.

The three-dimensional conformations of the phenobarbital and *N*-methylphenobarbital molecules are similar to that of phenytoin. Both compounds possess a phenyl ring and are active against partial seizures.

Mechanism of Action

The exact mechanism of action of phenobarbital is unknown, but enhancement of inhibitory processes and diminution of excitatory transmission probably contribute significantly. Recent data indicate that phenobarbital may selectively suppress abnormal neurons, inhibiting the spread and suppressing firing from the foci. Like phenytoin, phenobarbital suppresses high-frequency repetitive firing in neurons in culture through an action on Na^+ conductance, but only at high concentrations. Also at high concentrations, barbiturates block some Ca^{2+} currents (L-type and N-type). Phenobarbital binds to an allosteric regulatory site on the $GABA_A$ receptor, and it enhances the GABA receptor-mediated current by prolonging the openings of the Cl^- channels (see Chapter 22). Phenobarbital can also decrease excitatory responses. An effect on glutamate release is probably more significant than blockade of AMPA responses (see Chapter 21). Both the enhancement of GABA-mediated inhibition and the reduction of glutamate-mediated excitation are seen with therapeutically relevant concentrations of phenobarbital.

Clinical Uses

Phenobarbital is useful in the treatment of partial seizures and generalized tonic-clonic seizures, although the drug is often tried for virtually every seizure type, especially when attacks are difficult to control. There is little evidence for its effectiveness in generalized seizures such as absence, atonic attacks, and infantile spasms; it may worsen certain patients with these seizure types.

Some physicians prefer either metharbital (no longer readily available) or mephobarbital (especially the latter) to phenobarbital because of supposed decreased adverse effects. Only anecdotal data are available to support such comparisons.

Pharmacokinetics, Therapeutic Levels, & Dosage

For pharmacokinetics, drug interactions, and toxicity of phenobarbital, see Chapter 22.

The therapeutic levels of phenobarbital in most patients range from 10 mcg/mL to 40 mcg/mL. Documentation of effectiveness is best in febrile seizures, and levels below 15 mcg/mL appear ineffective for prevention of febrile seizure recurrence. The upper end of the therapeutic range is more difficult to define because many patients appear to tolerate chronic levels above 40 mcg/mL.

PRIMIDONE

Primidone, or 2-desoxyphenobarbital (Figure 24–6), was first marketed in the early 1950s. It was later reported that primidone was metabolized to phenobarbital and phenylethylmalonamide (PEMA). All three compounds are active anticonvulsants.

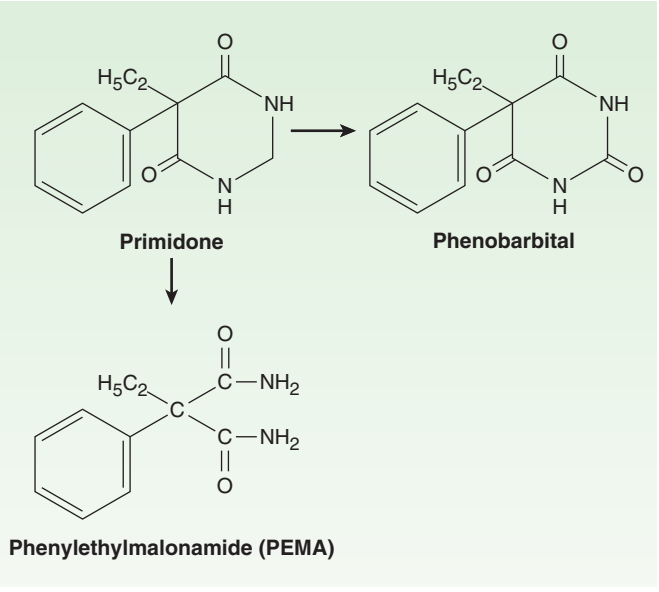


FIGURE 24–6 Primidone and its active metabolites.

Mechanism of Action

Although primidone is converted to phenobarbital, the mechanism of action of primidone itself may be more like that of phenytoin.

Clinical Uses

Primidone, like its metabolites, is effective against partial seizures and generalized tonic-clonic seizures and may be more effective than phenobarbital. It was previously considered to be the drug of choice for complex partial seizures, but later studies of partial seizures in adults strongly suggest that carbamazepine and phenytoin are superior to primidone. Attempts to determine the relative potencies of the parent drug and its two metabolites have been conducted in newborn infants, in whom drug-metabolizing enzyme systems are very immature and in whom primidone is only slowly metabolized. Primidone has been shown to be effective in controlling seizures in this group and in older patients beginning treatment with primidone; older patients show seizure control before phenobarbital concentrations reach the therapeutic range. Finally, studies of maximal electroshock seizures in animals suggest that primidone has an anticonvulsant action independent of its conversion to phenobarbital and PEMA (the latter is relatively weak).

Pharmacokinetics

Primidone is completely absorbed, usually reaching peak concentrations about 3 hours after oral administration, although considerable variation has been reported. Primidone is generally distributed in total body water, with a volume of distribution of 0.6 L/kg. It is not highly bound to plasma proteins; approximately 70% circulates as unbound drug.

Primidone is metabolized by oxidation to phenobarbital, which accumulates very slowly, and by scission of the heterocyclic ring to form PEMA (Figure 24–6). Both primidone and phenobarbital also undergo subsequent conjugation and excretion.

Primidone has a larger clearance than most other antiseizure drugs (2 L/kg/d), corresponding to a half-life of 6–8 hours. PEMA clearance is approximately half that of primidone, but phenobarbital has a very low clearance (see Table 3–1). The appearance of phenobarbital corresponds to the disappearance of primidone. Phenobarbital therefore accumulates very slowly but eventually reaches therapeutic concentrations in most patients when therapeutic doses of primidone are administered. During chronic therapy, phenobarbital levels derived from primidone are usually two to three times higher than primidone levels.

Therapeutic Levels & Dosage

Primidone is most efficacious when plasma levels are in the range of 8–12 mcg/mL. Concomitant levels of its metabolite, phenobarbital, at steady state usually vary from 15 to 30 mcg/mL. Dosages of 10–20 mg/kg/d are necessary to obtain these levels. It is very important, however, to start primidone at low doses and gradually increase over days to a few weeks to avoid prominent sedation and gastrointestinal complaints. When adjusting doses of the drug, it is important to remember that the parent drug reaches steady state rapidly (30–40 hours), but the active metabolites phenobarbital (20 days) and PEMA (3–4 days) reach steady state much more slowly.

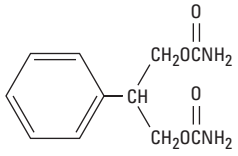
Toxicity

The dose-related adverse effects of primidone are similar to those of its metabolite, phenobarbital, except that drowsiness occurs early in treatment and may be prominent if the initial dose is too large. Gradual increments are indicated when starting the drug in either children or adults.

FELBAMATE

Felbamate has been approved and marketed in the USA and in some European countries. Although it is effective in some patients with partial seizures, the drug causes aplastic anemia and severe hepatitis at unexpectedly high rates and has been relegated to the status of a third-line drug for refractory cases.

Felbamate appears to have multiple mechanisms of action. It produces a use-dependent block of the NMDA receptor, with selectivity for the NR1-2B subtype. It also produces a barbiturate-like potentiation of $GABA_A$ receptor responses. Felbamate has a half-life of 20 hours (somewhat shorter when administered with either phenytoin or carbamazepine) and is metabolized by hydroxylation and conjugation; a significant percentage of the drug is excreted unchanged in the urine. When added to treatment with other antiseizure drugs, felbamate increases plasma phenytoin and valproic acid levels but decreases levels of carbamazepine.

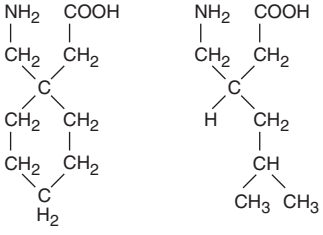


Felbamate

In spite of the seriousness of the adverse effects, thousands of patients worldwide utilize this medication. Usual dosages are 2000–4000 mg/d in adults, and effective plasma levels range from 30 mcg/mL to 100 mcg/mL. In addition to its usefulness in partial seizures, felbamate has proved effective against the seizures that occur in Lennox-Gastaut syndrome.

GABAPENTIN & PREGABALIN

Gabapentin is an amino acid, an analog of GABA, that is effective against partial seizures. Originally planned as a spasmolytic, it was found to be more effective as an antiseizure drug. Pregabalin is another GABA analog, closely related to gabapentin. This drug has been approved for both antiseizure activity and for its analgesic properties.



Gabapentin Pregabalin

Mechanism of Action

In spite of their close structural resemblance to GABA, gabapentin and pregabalin do not act directly on GABA receptors. They may, however, modify the synaptic or nonsynaptic release of GABA. An increase in brain GABA concentration is observed in patients receiving gabapentin. Gabapentin is transported into the brain by the L-amino acid transporter. Gabapentin and pregabalin bind avidly to the $\alpha_2\delta$ subunit of voltage-gated Ca^{2+} channels. This appears to underlie the main mechanism of action, which is decreasing Ca^{2+} entry, with a predominant effect on presynaptic N-type channels. A decrease in the synaptic release of glutamate provides the antiepileptic effect.

Clinical Uses

Gabapentin is effective as an adjunct against partial seizures and generalized tonic-clonic seizures at dosages that range up to 2400 mg/d in controlled clinical trials. Open follow-up studies permitted dosages up to 4800 mg/d, but data are inconclusive on the effectiveness or tolerability of such doses. Monotherapy studies also document some efficacy. Some clinicians have found that very high dosages are needed to achieve improvement in seizure control. Effectiveness in other seizure types has not been well demonstrated. Gabapentin has also been promoted for the treatment of neuropathic pain and is now indicated for postherpetic neuralgia in adults at doses of 1800 mg and above. The most common adverse effects are somnolence, dizziness, ataxia, headache, and tremor.

Pregabalin is approved for the adjunctive treatment of partial seizures, with or without secondary generalization; controlled clinical trials have documented its effectiveness. It is available only in oral form, and the dosage ranges from 150 to 600 mg/d, usually in two or three divided doses. Pregabalin is also approved for use in neuropathic pain, including painful diabetic peripheral neuropathy and postherpetic neuralgia. It is the first drug in the USA approved for fibromyalgia. In Europe it is approved for generalized anxiety disorder.

Pharmacokinetics

Gabapentin is not metabolized and does not induce hepatic enzymes. Absorption is nonlinear and dose-dependent at very high doses, but the elimination kinetics are linear. The drug is not bound to plasma proteins. Drug-drug interactions are negligible. Elimination is via renal mechanisms; the drug is excreted unchanged. The half-life is relatively short, ranging from 5 to 8 hours; the drug is typically administered two or three times per day.

Pregabalin, like gabapentin, is not metabolized and is almost entirely excreted unchanged in the urine. It is not bound to plasma proteins and has virtually no drug-drug interactions, again resembling the characteristics of gabapentin. Likewise, other drugs do not affect the pharmacokinetics of pregabalin. The half-life of pregabalin ranges from about 4.5 hours to 7.0 hours, thus requiring more than once-daily dosing in most patients.

LACOSAMIDE

Lacosamide is an amino acid-related compound that has been studied in both pain syndromes and partial seizures. The drug was approved in Europe and the USA in 2008 for the treatment of partial seizures.

Mechanism of Action

Activity resides in the *R*(–) enantiomer. Two effects relevant to the mechanism of action of lacosamide as an antiseizure drug have been described. Lacosamide enhances *slow* inactivation of voltage-gated Na^+ channels (in contrast to the prolongation of fast inactivation shown by other AEDs). It also binds to the collapsin-response mediator protein, CRMP-2, thereby blocking the effect of neurotrophic factors such as BDNF and NT3 on axonal and dendritic growth.

Clinical Uses

Lacosamide is approved as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients with epilepsy who are age 16–17 years and older. Clinical

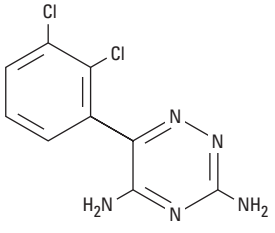
trials include three multicenter, randomized placebo-controlled studies with more than 1300 patients. Treatment was effective at both 200 and 400 mg/d. Adverse effects were dizziness, headache, nausea, and diplopia. In the open-label follow-up study, at dosages ranging from 100 to 800 mg/d, many patients continued lacosamide treatment for 24 to 30 months. The drug is typically administered twice daily, beginning with 50 mg doses and increasing by 100 mg increments weekly. An intravenous formulation provides short-term replacement for the oral drug.

Pharmacokinetics

Oral lacosamide is rapidly and completely absorbed in adults, with no food effect. Bioavailability is nearly 100%. The plasma concentrations are proportional to dosage up to 800 mg orally. Peak concentrations occur from 1 to 4 hours after oral dosing, with an elimination half-life of 13 hours. There are no active metabolites and protein binding is minimal. Lacosamide does not induce or inhibit cytochrome P450 isoenzymes, so drug interactions are negligible.

LAMOTRIGINE

Lamotrigine was developed when some investigators thought that the antifolate effects of certain antiseizure drugs (eg, phenytoin) might contribute to their effectiveness. Several phenyltriazines were developed, and though their antifolate properties were weak, some were active in seizure screening tests.



Lamotrigine

Mechanism of Action

Lamotrigine, like phenytoin, suppresses sustained rapid firing of neurons and produces a voltage- and use-dependent blockade of Na^+ channels. This action probably explains lamotrigine's efficacy in focal epilepsy. It appears likely that lamotrigine also inhibits voltage-gated Ca^{2+} channels, particularly the N- and P/Q-type channels, which would account for its efficacy in primary generalized seizures in childhood, including absence attacks. Lamotrigine also decreases the synaptic release of glutamate.

Clinical Uses

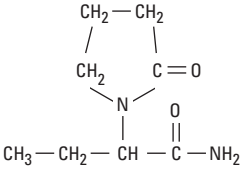
Although most controlled studies have evaluated lamotrigine as add-on therapy, it is generally agreed that the drug is effective as monotherapy for partial seizures, and lamotrigine is now widely prescribed for this indication. The drug is also active against absence and myoclonic seizures in children and is approved for seizure control in the Lennox-Gastaut syndrome. Lamotrigine is also effective for bipolar disorder. Adverse effects include dizziness, headache, diplopia, nausea, somnolence, and skin rash. The rash is considered a typical hypersensitivity reaction. Although the risk of rash may be diminished by introducing the drug slowly, pediatric patients are at greatest risk, some studies suggest that a potentially life-threatening dermatitis will develop in 1–2% of pediatric patients.

Pharmacokinetics

Lamotrigine is almost completely absorbed and has a volume of distribution in the range of 1–1.4 L/kg. Protein binding is only about 55%. The drug has linear kinetics and is metabolized primarily by glucuronidation to the 2-*N*-glucuronide, which is excreted in the urine. Lamotrigine has a half-life of approximately 24 hours in normal volunteers; this decreases to 13–15 hours in patients taking enzyme-inducing drugs. Lamotrigine is effective against partial seizures in adults at dosages typically between 100 and 300 mg/d and with a therapeutic blood level near 3 mcg/mL. Valproate causes a twofold increase in the drug's half-life; in patients receiving valproate, the initial dosage of lamotrigine must be reduced to 25 mg every other day.

LEVETIRACETAM

Levetiracetam is a piracetam analog that is ineffective against seizures induced by maximum electroshock or pentylenetetrazol but has prominent activity in the kindling model. This is the first major drug with this unusual preclinical profile that is effective against partial seizures.



Levetiracetam

Mechanism of Action

Levetiracetam binds selectively to the synaptic vesicular protein SV_2A. The function of this protein is not understood but it is likely that levetiracetam modifies the synaptic release of glutamate and GABA through an action on vesicular function.

Clinical Uses

Levetiracetam is marketed for the adjunctive treatment of partial seizures in adults and children for primary generalized tonic-clonic seizures and for the myoclonic seizures of juvenile myoclonic epilepsy. Adult dosing can begin with 500 or 1000 mg/d. The dosage can be increased every 2–4 weeks by 1000 mg to a maximum dosage of 3000 mg/d. The drug is dosed twice daily. Adverse effects include somnolence, asthenia, ataxia, and dizziness. Less common but more

serious are mood and behavioral changes; psychotic reactions are rare. Drug interactions are minimal; levetiracetam is not metabolized by cytochrome P450. Oral formulations include extended-release tablets; an intravenous preparation is also available.

Pharmacokinetics

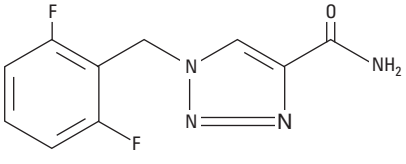
Oral absorption of levetiracetam is nearly complete; it is rapid and unaffected by food, with peak plasma concentrations in 1.3 hours. Kinetics are linear. Protein binding is less than 10%. The plasma half-life is 6–8 hours, but may be longer in the elderly. Two thirds of the drug is excreted unchanged in the urine; the drug has no known active metabolites.

RETIGABINE (EZOGABINE)

Retigabine (ezogabine in the USA) was approved as an anti-seizure drug in Europe and the USA in 2010. It is a potassium-channel facilitator and unique in its mechanism of action. Absorption is not affected by food and kinetics are linear; drug interactions are minimal. Clinical trials demonstrated efficacy in partial seizures, and approval is for the adjunctive treatment of partial-onset seizures in adults. Doses range from 600 to 1200 mg/day, with 900 mg/day expected to be the median. The current dosage form requires three-times-per-day administration, and the dose must be titrated in most patients. Most adverse effects are dose-related and include dizziness, somnolence, blurred vision, confusion, and dysarthria. Bladder dysfunction, mostly mild and related to the drug's mechanism of action, was observed in 8-9% of patients in the clinical trials.

RUFINAMIDE

Rufinamide is a triazole derivative with little similarity to other antiseizure drugs.



Rufinamide

Mechanism of Action

Rufinamide is protective in the maximal electroshock and pentylenetetrazol tests in rats and mice. It decreases sustained high-frequency firing of neurons in vitro and is thought to prolong the inactive state of the Na^+ channel. Significant interactions with GABA systems or metabotropic glutamate receptors have not been seen.

Clinical Uses

Rufinamide is approved in the USA for adjunctive treatment of seizures associated with the Lennox-Gastaut syndrome in patients age 4 years and older. The drug is effective against all seizure types in this syndrome and specifically against tonic-atonic seizures. Recent data also suggest it may be effective against partial seizures. Treatment in children is typically started at 10 mg/kg/d in two equally divided doses and gradually increased to 45 mg/kg/d or 3200 mg/d, whichever is lower. Adults can begin with 400–800 mg/d in two equally divided doses up to a maximum of 3200 mg/d as tolerated. The drug should be given with food. The most common adverse events are somnolence, vomiting, pyrexia, and diarrhea.

Pharmacokinetics

Rufinamide is well absorbed, but plasma concentrations peak between 4 and 6 hours. The half-life is 6–10 hours, and minimal plasma protein binding is observed. Although cytochrome P450 enzymes are not involved, the drug is extensively metabolized to inactive products. Most of the drug is excreted in the urine; an acid metabolite accounts for about two thirds of the dose. In one study, rufinamide did not appear to significantly affect the plasma concentrations of other drugs used for the Lennox-Gastaut syndrome such as topiramate, lamotrigine, or valproic acid, but conflicting data suggest more robust interactions with other AEDs, including effects on rufinamide levels, especially in children.

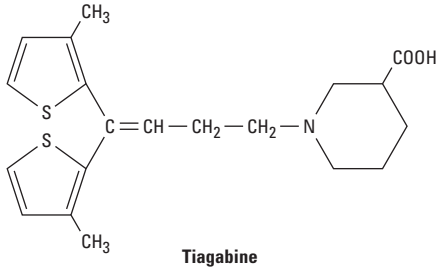
STIRIPENTOL

Stiripentol, though not a new molecule, was approved in Europe in 2007 for a very specific type of epilepsy. The drug is used with clobazam and valproate in the adjunctive therapy of refractory generalized tonic-clonic seizures in patients with severe myoclonic epilepsy of infancy (SMEI, Dravet's syndrome) whose seizures are not adequately controlled with clobazam and valproate. The drug is legally imported into the USA on a compassionate use basis. The mechanism of action of stiripentol is not well understood but it has been shown to enhance GABAergic transmission in the brain, partly through a barbiturate-like effect, ie, prolonged opening of the Cl^- channels in $GABA_A$ receptors. It also increases GABA levels in the brain. It can increase the effect of other AEDs by slowing their inactivation by cytochrome P450.

Stiripentol is a potent inhibitor of CYP3A4, CYP1A2, and CYP2C19. Adverse effects of stiripentol itself are few, but the drug can dramatically increase the levels of valproate, clobazam, and the active metabolite of the latter, norclobazam. These drugs must be used cautiously together to avoid adverse effects. Dosing is complex, typically beginning with a reduction of the concomitant medication; stiripentol is then started at 10 mg/kg/d and increased gradually to tolerability or to much higher doses. The kinetics of stiripentol are nonlinear.

TIAGABINE

Tiagabine is a derivative of nipecotic acid and was "rationally designed" as an inhibitor of GABA uptake (as opposed to discovery through random screening).



Tiagabine

Mechanism of Action

Tiagabine is an inhibitor of GABA uptake in both neurons and glia. It preferentially inhibits the transporter isoform 1 (GAT-1) rather than GAT-2 or GAT-3 and increases extracellular GABA levels in the forebrain and hippocampus where GAT-1 is preferentially expressed. It prolongs the inhibitory action of synaptically released GABA, but its most significant effect may be potentiation of tonic inhibition. In rodents, it is potent against kindled seizures but weak against the maximal electroshock model, consistent with its predominant action in the forebrain and hippocampus.

Clinical Uses

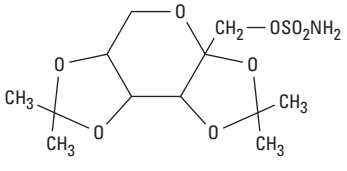
Tiagabine is indicated for the adjunctive treatment of partial seizures and is effective in doses ranging from 16 to 56 mg/d. Divided doses as often as four times daily are sometimes required. Minor adverse events are dose related and include nervousness, dizziness, tremor, difficulty in concentrating, and depression. Excessive confusion, somnolence, or ataxia may require discontinuation. Psychosis occurs rarely. The drug can *cause* seizures in some patients, notably those taking the drug for other indications. Rash is an uncommon idiosyncratic adverse effect.

Pharmacokinetics

Tiagabine is 90–100% bioavailable, has linear kinetics, and is highly protein bound. The half-life is 5–8 hours and decreases in the presence of enzyme-inducing drugs. Food decreases the peak plasma concentration but not the area under the concentration curve (see Chapter 3). Hepatic impairment causes a slight decrease in clearance and may necessitate a lower dose. The drug is oxidized in the liver by CYP3A. Elimination is primarily in the feces (60–65%) and urine (25%).

TOPIRAMATE

Topiramate is a substituted monosaccharide that is structurally different from all other antiseizure drugs.



Topiramate

Mechanism of Action

Topiramate blocks repetitive firing of cultured spinal cord neurons, as do phenytoin and carbamazepine. Its mechanism of action, therefore, is likely to involve blocking of voltage-gated Na^+ channels. It also acts on high-voltage activated (L-type) Ca^{2+} channels. Topiramate potentiates the inhibitory effect of GABA, acting at a site different from the benzodiazepine or barbiturate sites. Topiramate also depresses the excitatory action of kainate on glutamate receptors. The multiple effects of topiramate may arise through a primary action on kinases altering the phosphorylation of voltage-gated and ligand-gated ion channels.

Clinical Uses

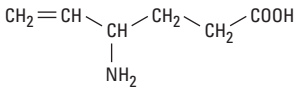
Clinical trials of topiramate as monotherapy demonstrated efficacy against partial and generalized tonic-clonic seizures. The drug is also approved for the Lennox-Gastaut syndrome, and may be effective in infantile spasms and even absence seizures. Topiramate is also approved for the treatment of migraine headaches. The use of the drug in psychiatric disorders is controversial; convincing controlled data are lacking. Dosages typically range from 200 to 600 mg/d, with a few patients tolerating dosages higher than 1000 mg/d. Most clinicians begin at a low dose (50 mg/d) and increase slowly to prevent adverse effects. Several studies have used topiramate in monotherapy with encouraging results. Although no idiosyncratic reactions have been noted, dose-related adverse effects occur most frequently in the first 4 weeks and include somnolence, fatigue, dizziness, cognitive slowing, paresthesias, nervousness, and confusion. Acute myopia and glaucoma may require prompt drug withdrawal. Urolithiasis has also been reported. The drug is teratogenic in animal models, and hypospadias has been reported in male infants exposed in utero to topiramate; no causal relationship, however, could be established.

Pharmacokinetics

Topiramate is rapidly absorbed (about 2 hours) and is 80% bioavailable. There is no food effect on absorption, minimal (15%) plasma protein binding, and only moderate (20–50%) metabolism; no active metabolites are formed. The drug is primarily excreted unchanged in the urine. The half-life is 20–30 hours. Although increased levels are seen with renal failure and hepatic impairment, there is no age or gender effect, no autoinduction, no inhibition of metabolism, and kinetics are linear. Drug interactions do occur and can be complex, but the major effect is on topiramate levels rather than on the levels of other antiseizure drugs. Birth control pills may be less effective in the presence of topiramate, and higher estrogen doses may be required.

VIGABATRIN

Current investigations that seek drugs to enhance the effects of GABA include efforts to find GABA agonists and prodrugs, GABA transaminase inhibitors, and GABA uptake inhibitors. Vigabatrin is one such drug.



Vigabatrin

Mechanism of Action

Vigabatrin is an irreversible inhibitor of GABA aminotransferase (GABA-T), the enzyme responsible for the degradation of GABA. It may also inhibit the vesicular GABA transporter. Vigabatrin produces a sustained increase in the extracellular concentration of GABA in the brain. This leads to some desensitization of synaptic $GABA_A$ receptors but prolonged activation of nonsynaptic $GABA_A$ receptors that provide tonic inhibition. A decrease in brain glutamine synthetase activity is probably secondary to the increased GABA concentrations. It is effective in a wide range of seizure models. Vigabatrin is marketed as a racemate; the *S*(+) enantiomer is active and the *R*(–) enantiomer appears to be inactive.

Clinical Uses

Vigabatrin is useful in the treatment of partial seizures and infantile spasms. The half-life is approximately 6–8 hours, but considerable evidence suggests that the pharmacodynamic activity of the drug is more prolonged and not well correlated with the plasma half-life. In infants, the dosage is 50–150 mg/d. In adults, vigabatrin should be started at an oral dosage of 500 mg twice daily; a total of 2–3 g (rarely more) daily may be required for full effectiveness.

Typical toxicities include drowsiness, dizziness, and weight gain. Less common but more troublesome adverse reactions are agitation, confusion, and psychosis; preexisting mental illness is a relative contraindication. The drug was delayed in its worldwide introduction by the appearance in rats and dogs of a reversible intramyelinic edema. This phenomenon has now been detected in infants taking the drug; the clinical significance is unknown. In addition, long-term therapy with vigabatrin has been associated with development of peripheral visual field defects in 30–50% of patients. The lesions are located in the retina, increase with drug exposure, and are usually not reversible. Newer techniques such as optical coherence tomography may better define the defect, which has proved difficult to quantify. Vigabatrin is usually reserved for use in patients with infantile spasms or with complex partial seizures refractory to other treatments.

ZONISAMIDE

Zonisamide is a sulfonamide derivative. Its primary site of action appears to be the Na^+ channel; it also acts on T-type voltage-gated Ca^{2+} channels. The drug is effective against partial and generalized tonic-clonic seizures and may also be useful against infantile spasms and certain myoclonias. It has good bioavailability, linear kinetics, low protein-binding, renal excretion, and a half-life of 1–3 days. Dosages range from 100 to 600 mg/d in adults and from 4 to 12 mg/d in children. Adverse effects include drowsiness, cognitive impairment, and potentially serious skin rashes. Zonisamide does not interact with other antiseizure drugs.

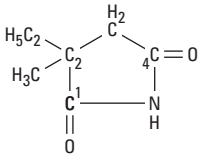
DRUGS USED IN GENERALIZED SEIZURES

ETHOSUXIMIDE

Ethosuximide was introduced in 1960 as the third of three marketed succinimides in the USA. Ethosuximide has very little activity against maximal electroshock but considerable efficacy against pentylenetetrazol seizures; it was introduced as a "pure petit mal" drug.

Chemistry

Ethosuximide is the last antiseizure drug to be marketed whose origin is in the cyclic ureide structure. The three antiseizure succinimides marketed in the USA are ethosuximide, phensuximide, and methsuximide. Methsuximide and phensuximide have phenyl substituents, whereas ethosuximide is 2-ethyl-2-methylsuccinimide.



Ethosuximide

Mechanism of Action

Ethosuximide has an important effect on Ca^{2+} currents, reducing the low-threshold (T-type) current. This effect is seen at therapeutically relevant concentrations in thalamic neurons. The T-type Ca^{2+} currents are thought to provide a pacemaker current in thalamic neurons responsible for generating the rhythmic cortical discharge of an absence attack. Inhibition of this current could therefore account for the specific therapeutic action of ethosuximide. A recently described effect on inwardly rectifying K^+ channels may also be significant.

Clinical Uses

As predicted from its activity in laboratory models, ethosuximide is particularly effective against absence seizures, but has a very narrow spectrum of clinical activity. Documentation of its effectiveness in human absence seizures was achieved with long-term electroencephalographic recording techniques. Data continue to show that ethosuximide and valproate are the drugs of choice for absence seizures and are more effective than lamotrigine.

Pharmacokinetics

Absorption is complete following administration of the oral dosage forms. Peak levels are observed 3–7 hours after oral administration of the capsules. Ethosuximide is not protein-bound. The drug is completely metabolized, principally by hydroxylation, to inactive metabolites. Ethosuximide has a very low total body clearance (0.25 L/kg/d). This corresponds to a half-life of approximately 40 hours, although values from 18 to 72 hours have been reported.

Therapeutic Levels & Dosage

Therapeutic levels of 60–100 mcg/mL can be achieved in adults with dosages of 750–1500 mg/d, although lower or higher dosages and blood levels (up to 125 mcg/mL) may be necessary and tolerated in some patients. Ethosuximide has a linear relationship between dose and steady-state plasma levels. The drug might be administered as a single daily dose were it not for its adverse gastrointestinal effects; twice-a-day dosage is common.

Drug Interactions & Toxicity

Administration of ethosuximide with valproic acid results in a decrease in ethosuximide clearance and higher steady-state concentrations owing to inhibition of metabolism. No other important drug interactions have been reported for the succinimides. The most common dose-related adverse effect of ethosuximide is gastric distress, including pain, nausea, and vomiting. When an adverse effect does occur, temporary dosage reductions may allow adaptation. Other dose-related adverse effects are transient lethargy or fatigue and, much less commonly, headache, dizziness, hiccup, and euphoria. Behavioral changes are usually in the direction of improvement. Non–dose-related or idiosyncratic adverse effects of ethosuximide are extremely uncommon.

PHENSUXIMIDE & METHSUXIMIDE

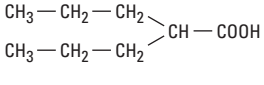
Phensuximide (no longer readily available) and methsuximide are phenylsuccinimides that were developed and marketed before ethosuximide. They are used primarily as anti-absence drugs. Methsuximide is generally considered more toxic, and phensuximide less effective, than ethosuximide. Unlike ethosuximide, these two compounds have some activity against maximal electroshock seizures, and methsuximide has been used for partial seizures by some investigators.

VALPROIC ACID & SODIUM VALPROATE

Sodium valproate, also used as the free acid, valproic acid, was found to have antiseizure properties when used as a solvent in the search for other drugs effective against seizures. It was marketed in France in 1969 but was not licensed in the USA until 1978. Valproic acid is fully ionized at body pH, and for that reason the active form of the drug may be assumed to be the valproate ion regardless of whether valproic acid or a salt of the acid is administered.

Chemistry

Valproic acid is one of a series of fatty carboxylic acids that have antiseizure activity; this activity appears to be greatest for carbon chain lengths of five to eight atoms. The amides and esters of valproic acid are also active antiseizure agents.



Valproic acid

Mechanism of Action

The time course of valproate's anticonvulsant activity appears to be poorly correlated with blood or tissue levels of the parent drug, an observation giving rise to considerable speculation regarding both the active species and the mechanism of action of valproic acid. Valproate is active against both pentylenetetrazol and maximal electroshock seizures. Like phenytoin and carbamazepine, valproate blocks sustained high-frequency repetitive firing of neurons in culture at therapeutically relevant concentrations. Its action against partial seizures may be a consequence of this effect on Na^+ currents. Blockade of NMDA receptor-mediated excitation may also be important. Much attention has been paid to the effects of valproate on GABA. Several studies have shown increased levels of GABA in the brain after administration of valproate, although the mechanism for this increase remains unclear. An effect of valproate to facilitate glutamic acid decarboxylase (GAD), the enzyme responsible for GABA synthesis, has been described. An inhibitory effect on the GABA transporter GAT-1 may contribute. At very high concentrations, valproate inhibits GABA transaminase in the brain, thus blocking degradation of GABA. However, at the relatively low doses of valproate needed to abolish pentylenetetrazol seizures, brain GABA levels may remain unchanged. Valproate produces a reduction in the aspartate content of rodent brain, but the relevance of this effect to its anticonvulsant action is not known.

Valproic acid is a potent inhibitor of histone deacetylase and through this mechanism changes the transcription of many genes. A similar effect, but to a lesser degree, is shown by some other antiseizure drugs (topiramate, carbamazepine, and a metabolite of levetiracetam).

Clinical Uses

Valproate is very effective against absence seizures and is often preferred to ethosuximide when the patient has concomitant generalized tonic-clonic attacks. Valproate is unique in its ability to control certain types of myoclonic seizures; in some cases the effect is very dramatic. The drug is effective in tonic-clonic seizures, especially those that are primarily generalized. A few patients with atonic attacks may also respond, and some evidence suggests that the drug is effective in partial seizures. Its use in epilepsy is at least as broad as that of any other drug. Intravenous formulations are occasionally used to treat status epilepticus.

Other uses of valproate include management of bipolar disorder and migraine prophylaxis.

Pharmacokinetics

Valproate is well absorbed after an oral dose, with bioavailability greater than 80%. Peak blood levels are observed within 2 hours. Food may delay absorption, and decreased toxicity may result if the drug is given after meals.

Valproic acid is 90% bound to plasma proteins, although the fraction bound is somewhat reduced at blood levels greater than 150 mcg/mL. Since valproate is both highly ionized and highly protein-bound, its distribution is essentially confined to extracellular water,

with a volume of distribution of approximately 0.15 L/kg. At higher doses, there is an increased free fraction of valproate, resulting in lower total drug levels than expected. It may be clinically useful, therefore, to measure both total and free drug levels. Clearance for valproate is low and dose dependent; its half-life varies from 9 to 18 hours. Approximately 20% of the drug is excreted as a direct conjugate of valproate.

The sodium salt of valproate is marketed in Europe as a tablet and is quite hygroscopic. In Central and South America, the magnesium salt is available, which is considerably less hygroscopic. The free acid of valproate was first marketed in the USA in a capsule containing corn oil; the sodium salt is also available in syrup, primarily for pediatric use. An enteric-coated tablet of divalproex sodium is also marketed in the USA. This improved product, a 1:1 coordination compound of valproic acid and sodium valproate, is as bioavailable as the capsule but is absorbed much more slowly and is preferred by many patients. Peak concentrations following administration of the enteric-coated tablets are seen in 3–4 hours. Various extended-release preparations are available; not all are bioequivalent and may require dosage adjustment.

Therapeutic Levels & Dosage

Dosages of 25–30 mg/kg/d may be adequate in some patients, but others may require 60 mg/kg/d or even more. Therapeutic levels of valproate range from 50 to 100 mcg/mL.

Drug Interactions

Valproate displaces phenytoin from plasma proteins. In addition to binding interactions, valproate inhibits the metabolism of several drugs, including phenobarbital, phenytoin, and carbamazepine, leading to higher steady-state concentrations of these agents. The inhibition of phenobarbital metabolism, for example, may cause levels of the barbiturate to rise steeply, causing stupor or coma. Valproate can dramatically decrease the clearance of lamotrigine.

Toxicity

The most common dose-related adverse effects of valproate are nausea, vomiting, and other gastrointestinal complaints such as abdominal pain and heartburn. The drug should be started gradually to avoid these symptoms. Sedation is uncommon with valproate alone but may be striking when valproate is added to phenobarbital. A fine tremor is frequently seen at higher levels. Other reversible adverse effects, seen in a small number of patients, include weight gain, increased appetite, and hair loss.

The idiosyncratic toxicity of valproate is largely limited to hepatotoxicity, but this may be severe; there seems little doubt that the hepatotoxicity of valproate has been responsible for more than 50 fatalities in the USA alone. The risk is greatest for patients under 2 years of age and for those taking multiple medications. Initial aspartate aminotransferase values may not be elevated in susceptible patients, although these levels do eventually become abnormal. Most fatalities have occurred within 4 months after initiation of therapy. Some clinicians recommend treatment with oral or intravenous L-carnitine as soon as severe hepatotoxicity is suspected. Careful monitoring of liver function is recommended when starting the drug; the hepatotoxicity is reversible in some cases if the drug is withdrawn. The other observed idiosyncratic response with valproate is thrombocytopenia, although documented cases of abnormal bleeding are lacking. It should be noted that valproate is an effective and popular antiseizure drug and that only a very small number of patients have had severe toxic effects from its use.

Several epidemiologic studies of valproate have confirmed a substantial increase in the incidence of spina bifida in the offspring of women who took valproate during pregnancy. In addition, an increased incidence of cardiovascular, orofacial, and digital abnormalities has been reported. These observations must be strongly considered in the choice of drugs during pregnancy.

OXAZOLIDINEDIONES

Trimethadione, the first oxazolidinedione (Figure 24–3), was introduced as an antiseizure drug in 1945 and remained the drug of choice for absence seizures until the introduction of succinimides in the 1950s. Use of the oxazolidinediones—trimethadione, paramethadione, and dimethadione—is now very limited; the latter two are not readily available.

These compounds are active against pentylenetetrazol-induced seizures. Trimethadione raises the threshold for seizure discharges after repetitive thalamic stimulation. It—or, more notably, its active metabolite dimethadione—has the same effect on thalamic Ca^{2+} currents as ethosuximide (reducing the T-type Ca^{2+} current). Thus, suppression of absence seizures is likely to depend on inhibiting the pacemaker action of thalamic neurons.

Trimethadione is rapidly absorbed, with peak levels reached within 1 hour after drug administration. It is not bound to plasma proteins. Trimethadione is completely metabolized in the liver by demethylation to dimethadione, which may exert the major antiseizure activity. Dimethadione has an extremely long half-life (240 hours). The therapeutic plasma level range for trimethadione has never been established, although trimethadione blood levels higher than 20 mcg/mL and dimethadione levels higher than 700 mcg/mL have been suggested. A dosage of 30 mg/kg/d of trimethadione is necessary to achieve these levels in adults.

The most common and bothersome dose-related adverse effect of the oxazolidinediones is sedation. Trimethadione has been associated with many other toxic adverse effects, some of which are severe. These drugs should not be used during pregnancy.

OTHER DRUGS USED IN MANAGEMENT OF EPILEPSY

Some drugs not classifiable by application to seizure type are discussed in this section.

BENZODIAZEPINES

Six benzodiazepines play prominent roles in the therapy of epilepsy (see also Chapter 22). Although many benzodiazepines are similar chemically, subtle structural alterations result in differences in activity and pharmacokinetics. They have two mechanisms of antiseizure action, which are shown to different degrees by the six compounds. This is evident from the fact that diazepam is relatively more potent against electroshock and clonazepam against pentylenetetrazol (the latter effect correlating with an action at the GABA-benzodiazepine allosteric receptor sites). Possible mechanisms of action are discussed in Chapter 22.

Diazepam given intravenously or rectally is highly effective for stopping continuous seizure activity, especially generalized tonic-clonic status epilepticus (see below). The drug is occasionally given orally on a long-term basis, although it is not considered very effective in this application, probably because of the rapid development of tolerance. A rectal gel is available for refractory patients who need acute control of bouts of seizure activity. **Lorazepam** appears in some studies to be more effective and longer acting than diazepam in the treatment of status epilepticus and is preferred by some experts.

Clonazepam is a long-acting drug with documented efficacy against absence seizures; on a milligram basis, it is one of the most potent antiseizure agents known. It is also effective in some cases of myoclonic seizures and has been tried in infantile spasms. Sedation is prominent, especially on initiation of therapy; starting doses should be small. Maximal tolerated doses are usually in the range of 0.1–0.2 mg/kg, but many weeks of gradually increasing daily doses may be needed to achieve these dosages in some patients. **Nitrazepam** is not marketed in the USA but is used in many other countries, especially for infantile spasms and myoclonic seizures. It is less potent than clonazepam, and superiority to that drug has not been documented.

Clorazepate dipotassium is approved in the USA as an adjunct to treatment of complex partial seizures in adults. Drowsiness and lethargy are common adverse effects, but as long as the drug is increased gradually, dosages as high as 45 mg/d can be given.

Clobazam is not available in the USA but is marketed in most countries and is widely used in a variety of seizure types. It is a 1,5-benzodiazepine (other marketed benzodiazepines are 1,4-benzodiazepines) and reportedly has less sedative potential than benzodiazepines marketed in the USA. Whether the drug has significant clinical advantages is not clear. It has a half-life of 18 hours and is effective at dosages of 0.5–1 mg/kg/d. It does interact with some other antiseizure drugs and causes adverse effects typical of the benzodiazepines; efficacy, in some patients, is limited by the development of tolerance. It has an active metabolite, norclobazam.

Pharmacokinetics

See Chapter 22.

Limitations

Two prominent aspects of benzodiazepines limit their usefulness. The first is their pronounced sedative effect, which is unfortunate both in the treatment of status epilepticus and in chronic therapy. Children may manifest a paradoxical hyperactivity, as with barbiturates. The second problem is tolerance, in which seizures may respond initially but recur within a few months. The remarkable antiseizure potency of these compounds often cannot be realized because of these limiting factors.

ACETAZOLAMIDE

Acetazolamide is a diuretic whose main action is the inhibition of carbonic anhydrase (see Chapter 15). Mild acidosis in the brain may be the mechanism by which the drug exerts its antiseizure activity; alternatively, the depolarizing action of bicarbonate ions moving out of neurons via GABA receptor ion channels may be diminished by carbonic anhydrase inhibition. Acetazolamide has been used for all types of seizures but is severely limited by the rapid development of tolerance, with return of seizures usually within a few weeks. The drug may have a special role in epileptic women who experience seizure exacerbations at the time of menses; seizure control may be improved and tolerance may not develop because the drug is not administered continuously. The usual dosage is approximately 10 mg/kg/d to a maximum of 1000 mg/d.

Another carbonic anhydrase inhibitor, **sulthiame,** was not found to be effective as an anticonvulsant in clinical trials in the USA. It is marketed in a number of other countries.

CLINICAL PHARMACOLOGY OF ANTISEIZURE DRUGS

SEIZURE CLASSIFICATION

In general, the type of medication used for epilepsy depends on the empiric nature of the seizure. For this reason, considerable effort has been expended to classify seizures so that clinicians will be able to make a "seizure diagnosis" and on that basis prescribe appropriate therapy. Errors in seizure diagnosis cause use of the wrong drugs, and an unpleasant cycle ensues in which poor seizure control is followed by increasing drug doses and medication toxicity. As noted, seizures are divided into two groups: partial and generalized. Drugs used for partial seizures are more or less the same for all subtypes of partial seizures, but drugs used for generalized seizures are determined by the individual seizure subtype. A summary of the international classification of epileptic seizures is presented in Table 24–1.

Partial Seizures

Partial seizures are those in which a localized onset of the attack can be ascertained, either by clinical observation or by electroencephalographic recording; the attack begins in a specific locus in the brain. There are three types of partial seizures, determined to some extent by the degree of brain involvement by the abnormal discharge.

The least complicated partial seizure is the **simple partial seizure,** characterized by minimal spread of the abnormal discharge such that normal consciousness and awareness are preserved. For example, the patient may have a sudden onset of clonic jerking of an extremity lasting 60–90 seconds; residual weakness may last for 15–30 minutes after the attack. The patient is completely aware of the attack and can describe it in detail. The electroencephalogram may show an abnormal discharge highly localized to the involved portion of the brain.

The **complex partial seizure** also has a localized onset, but the discharge becomes more widespread (usually bilateral) and almost always involves the limbic system. Most complex partial seizures arise from one of the temporal lobes, possibly because of the susceptibility of this area of the brain to insults such as hypoxia or infection. Clinically, the patient may have a brief warning followed by an alteration of consciousness during which some patients stare and others stagger or even fall. Most, however, demonstrate fragments of integrated motor behavior called **automatisms** for which the patient has no memory. Typical automatisms are lip smacking, swallowing, fumbling, scratching, and even walking about. After 30–120 seconds, the patient makes a gradual recovery to normal consciousness but may feel tired or ill for several hours after the attack.

The last type of partial seizure is the **secondarily generalized attack,** in which a partial seizure immediately precedes a generalized tonic-clonic (grand mal) seizure. This seizure type is described in the text that follows.

Generalized Seizures

Generalized seizures are those in which there is no evidence of localized onset. The group is quite heterogeneous.

Generalized tonic-clonic (grand mal) seizures are the most dramatic of all epileptic seizures and are characterized by tonic rigidity of all extremities, followed in 15–30 seconds by a tremor that is actually an interruption of the tonus by relaxation. As the relaxation phases become longer, the attack enters the clonic phase, with massive jerking of the body. The clonic jerking slows over 60–120 seconds, and the patient is usually left in a stuporous state. The tongue or cheek may be bitten, and urinary incontinence is common. Primary generalized tonic-clonic seizures begin without evidence of localized onset, whereas secondary generalized tonic-clonic seizures are preceded by another seizure type, usually a partial seizure. The medical treatment of both primary and secondary generalized tonic-clonic seizures is the same and uses drugs appropriate for *partial* seizures.

The **absence (petit mal) seizure** is characterized by both sudden onset and abrupt cessation. Its duration is usually less than 10 seconds and rarely more than 45 seconds. Consciousness is altered; the attack may also be associated with mild clonic jerking of the eyelids or extremities, with postural tone changes, autonomic phenomena, and automatisms. The occurrence of automatisms can complicate the clinical differentiation from complex partial seizures in some patients. Absence attacks begin in childhood or adolescence and may occur up to hundreds of times a day. The electroencephalogram during the seizure shows a highly characteristic 2.5–3.5 Hz spike-and-wave pattern. Atypical absence patients have seizures with postural changes that are more abrupt, and such patients are often mentally retarded; the electroencephalogram may show a slower spike-and-wave discharge, and the seizures may be more refractory to therapy.

Myoclonic jerking is seen, to a greater or lesser extent, in a wide variety of seizures, including generalized tonic-clonic seizures, partial seizures, absence seizures, and infantile spasms. Treatment of seizures that include myoclonic jerking should be directed at the primary seizure type rather than at the myoclonus. Some patients, however, have myoclonic jerking as the major seizure type, and some have frequent myoclonic jerking and occasional generalized tonic-clonic seizures without overt signs of neurologic deficit. Many kinds of myoclonus exist, and much effort has gone into attempts to classify this entity.

Atonic seizures are those in which the patient has sudden loss of postural tone. If standing, the patient falls suddenly to the floor and may be injured. If seated, the head and torso may suddenly drop forward. Although most often seen in children, this seizure type is not unusual in adults. Many patients with atonic seizures wear helmets to prevent head injury. Momentary *increased* tone may be observed in some patients, hence the use of the term "tonic-atonic seizure."

Infantile spasms are an epileptic syndrome and not a seizure type. The attacks, though sometimes fragmentary, are most often bilateral and are included for pragmatic purposes with the generalized seizures. These attacks are most often characterized clinically by brief, recurrent myoclonic jerks of the body with sudden flexion or extension of the body and limbs; the forms of infantile spasms are, however, quite heterogeneous. Ninety percent of affected patients have their first attack before the age of 1 year. Most patients are intellectually delayed, presumably from the same cause as the spasms. The cause is unknown in many patients, but such widely disparate disorders as infection, kernicterus, tuberous sclerosis, and hypoglycemia have been implicated. In some cases, the electroencephalogram is characteristic. Drugs used to treat infantile spasms are effective only in some patients; there is little evidence that the cognitive retardation is alleviated by therapy, even when the attacks disappear.

THERAPEUTIC STRATEGY

In designing a therapeutic strategy, the use of a single drug is preferred, especially in patients who are not severely affected and who can benefit from the advantage of fewer adverse effects using monotherapy. For patients with hard-to-control seizures, multiple drugs are usually utilized simultaneously.

For most of the older antiseizure drugs, relationships between blood levels and therapeutic effects have been characterized to a high degree. The same is true for the pharmacokinetics of these drugs. These relationships provide significant advantages in the development of therapeutic strategies for the treatment of epilepsy. The therapeutic index for most antiseizure drugs is low, and toxicity is not uncommon. Thus, effective treatment of seizures often requires an awareness of the therapeutic levels and pharmacokinetic

TABLE 24–2 Serum concentrations reference ranges for some antiseizure drugs.

Antiseizure Drug	Reference Range (μmol/L)[1]	Conversion Factor (F)[2]
OLDER DRUGS		
Carbamazepine	15–45	4.23
Clobazam	0.1–1.0	3.32
Clonazepam	60–220 nmol/L	3.17
Ethosuximide	300–600	7.08
Phenytoin	40–80	3.96
Phenobarbital	50–130	4.31
Valproate	300–600	7.08
NEWER DRUGS (Post-1990)		
Felbamate	125–250	4.20
Gabapentin	70–120	5.83
Lamotrigine	10–60	3.90
Levetiracetam	30–240	5.88
Oxcarbazepine[3]	50–140	3.96
Pregabalin[4]	1–50	6.33
Tiagabine	50–250 nmol/L	2.43
Topiramate	15–60	2.95
Zonisamide	45–180	4.71

[1] These data are provided only as a general guideline. Many patients will respond better at different levels and some patients may have drug-related adverse events within the listed average therapeutic ranges.
[2] To convert to mcg/mL or mg/L, divide μmol/L by the conversion factor F.
[3] Monohydroxy- metabolite.
[4] Not well established.
Modified and updated, with permission, from Johannessen SI, Landmark CJ: Value of therapeutic drug monitoring in epilepsy. Expert Rev Neurother 2008;8: 929.

properties as well as the characteristic toxicities of each agent. Measurements of antiseizure drug plasma levels can be very useful when combined with clinical observations and pharmacokinetic data (Table 24–2). The relationship between seizure control and plasma drug levels is variable and often less clear for the drugs marketed since 1990.

MANAGEMENT OF EPILEPSY

PARTIAL SEIZURES & GENERALIZED TONIC-CLONIC SEIZURES

For many years, the choice of drugs for partial and tonic-clonic seizures was usually limited to phenytoin, carbamazepine, or barbiturates. There was a strong tendency to limit the use of sedative antiseizure drugs such as barbiturates and benzodiazepines to patients who could not tolerate other medications; this trend led, in the 1980s, to increased use of carbamazepine. Although carbamazepine and phenytoin remain widely used, most newer drugs (marketed after 1990) are effective against these same seizure types. With the older drugs, efficacy and long-term adverse effects are well established; this creates a confidence level in spite of questionable tolerability. Most newer drugs have a broader spectrum of activity, and many are well tolerated; therefore, the newer drugs are often preferred to the older ones. Although some data suggest that most of these newer drugs confer an increased risk of nontraumatic fractures, choosing a drug on this basis is not yet practical.

GENERALIZED SEIZURES

The issues (described above) related to choosing between old and new drugs apply to the generalized group of seizures as well.

The drugs used for generalized tonic-clonic seizures are the same as for partial seizures; in addition, valproate is clearly useful.

At least three drugs are effective against absence seizures. Two are nonsedating and therefore preferred: ethosuximide and valproate. Clonazepam is also highly effective but has disadvantages of dose-related adverse effects and development of tolerance. Lamotrigine and topiramate may also be useful.

Specific myoclonic syndromes are usually treated with valproate; an intravenous formulation can be used acutely if needed. It is nonsedating and can be dramatically effective. Other patients

respond to clonazepam, nitrazepam, or other benzodiazepines, although high doses may be necessary, with accompanying drowsiness. Zonisamide and levetiracetam may be useful. Another specific myoclonic syndrome, juvenile myoclonic epilepsy, can be aggravated by phenytoin or carbamazepine; valproate is the drug of choice followed by lamotrigine and topiramate.

Atonic seizures are often refractory to all available medications, although some reports suggest that valproate may be beneficial, as may lamotrigine. Benzodiazepines have been reported to improve seizure control in some of these patients but may worsen the attacks in others. Felbamate has been demonstrated to be effective in some patients, although the drug's idiosyncratic toxicity limits its use. If the loss of tone appears to be part of another seizure type (eg, absence or complex partial seizures), every effort should be made to treat the other seizure type vigorously, hoping for simultaneous alleviation of the atonic component of the seizure. The ketogenic diet may also be useful.

DRUGS USED IN INFANTILE SPASMS

The treatment of infantile spasms is unfortunately limited to improvement of control of the seizures rather than other features of the disorder, such as retardation. Most patients receive a course of intramuscular corticotropin, although some clinicians note that prednisone may be equally effective and can be given orally. Clinical trials have been unable to settle the matter. In either case, therapy must often be discontinued because of adverse effects. If seizures recur, repeat courses of corticotropin or corticosteroids can be given, or other drugs may be tried. A repository corticotropin for injection is now approved in the USA for the treatment of infantile spasms, either of cryptogenic or symptomatic etiology. Other drugs widely used are the benzodiazepines such as clonazepam or nitrazepam; their efficacy in this heterogeneous syndrome may be nearly as good as that of corticosteroids. Vigabatrin is effective and is considered the drug of choice by many pediatric neurologists. The mechanism of action of corticosteroids or corticotropin in the treatment of infantile spasms is unknown but may involve reduction in inflammatory processes.

STATUS EPILEPTICUS

There are many forms of status epilepticus. The most common, generalized tonic-clonic status epilepticus, is a life-threatening emergency, requiring immediate cardiovascular, respiratory, and metabolic management as well as pharmacologic therapy. The latter virtually always requires intravenous administration of antiseizure medications. Diazepam is the most effective drug in most patients for stopping the attacks and is given directly by intravenous push to a maximum total dose of 20–30 mg in adults. Intravenous diazepam may depress respiration (less frequently, cardiovascular function), and facilities for resuscitation must be immediately at hand during its administration. The effect of diazepam is not lasting, but the 30- to 40-minute seizure-free interval allows more definitive therapy to be initiated. Some physicians prefer lorazepam, which is equivalent to diazepam in effect and perhaps somewhat longer acting. For patients who are not actually in the throes of a seizure, diazepam therapy can be omitted and the patient treated at once with a long-acting drug such as phenytoin.

Until the introduction of fosphenytoin, the mainstay of continuing therapy for status epilepticus was intravenous phenytoin, which is effective and nonsedating. It can be given as a loading dose of 13–18 mg/kg in adults; the usual error is to give too little. Administration should be at a maximum rate of 50 mg/min. It is safest to give the drug directly by intravenous push, but it can also be diluted in saline; it precipitates rapidly in the presence of glucose. Careful monitoring of cardiac rhythm and blood pressure is necessary, especially in elderly people. At least part of the cardiotoxicity is from the propylene glycol in which the phenytoin is dissolved. Fosphenytoin, which is freely soluble in intravenous solutions without the need for propylene glycol or other solubilizing agents, is a safer parenteral agent. Because of its greater molecular weight, this prodrug is two thirds to three quarters as potent as phenytoin on a milligram basis.

In previously treated epileptic patients, the administration of a large loading dose of phenytoin may cause some dose-related toxicity such as ataxia. This is usually a relatively minor problem during the acute status episode and is easily alleviated by later adjustment of plasma levels.

For patients who do not respond to phenytoin, phenobarbital can be given in large doses: 100–200 mg intravenously to a total of 400–800 mg. Respiratory depression is a common complication, especially if benzodiazepines have already been given, and there should be no hesitation in instituting intubation and ventilation.

Although other drugs such as lidocaine have been recommended for the treatment of generalized tonic-clonic status epilepticus, general anesthesia is usually necessary in highly resistant cases.

For patients in absence status, benzodiazepines are still drugs of first choice. Rarely, intravenous valproate may be required.

SPECIAL ASPECTS OF THE TOXICOLOGY OF ANTISEIZURE DRUGS

TERATOGENICITY

The potential teratogenicity of antiseizure drugs is controversial and important. It is important because teratogenicity resulting from long-term drug treatment of millions of people throughout the world may have a profound effect even if the effect occurs in only a small percentage of cases. It is controversial because both epilepsy and antiseizure drugs are heterogeneous, and few epileptic patients are available for study who are not receiving these drugs. Furthermore, patients with severe epilepsy, in whom genetic factors rather than drug factors may be of greater importance in the occurrence of fetal malformations, are often receiving multiple antiseizure drugs in high doses.

In spite of these limitations, it appears—from whatever cause—that children born to mothers taking antiseizure drugs have an increased risk, perhaps twofold, of congenital malformations. Phenytoin has been implicated in a specific syndrome called **fetal hydantoin syndrome,** although not all investigators are convinced of its existence and a similar syndrome has been attributed both to phenobarbital and to carbamazepine. Valproate, as noted above, has also been implicated in a specific malformation, spina bifida. It is estimated that a pregnant woman taking valproic acid or sodium valproate has a 1–2% risk of having a child with spina bifida. Topiramate has shown some teratogenicity in animal testing and, as noted earlier, in the human male fetus.

In dealing with the clinical problem of a pregnant woman with epilepsy, most epileptologists agree that although it is important to minimize exposure to antiseizure drugs, both in numbers and dosages, it is also important not to allow maternal seizures to go unchecked.

WITHDRAWAL

Withdrawal of antiseizure drugs, whether by accident or by design, can cause increased seizure frequency and severity. The two factors to consider are the effects of the withdrawal itself and the need for continued drug suppression of seizures in the individual patient. In many patients, both factors must be considered. It is important to note, however, that the abrupt discontinuance of antiseizure drugs ordinarily does not cause seizures in nonepileptic patients, provided that the drug levels are not above the usual therapeutic range when the drug is stopped.

Some drugs are more easily withdrawn than others. In general, withdrawal of anti-absence drugs is easier than withdrawal of drugs needed for partial or generalized tonic-clonic seizures. Barbiturates and benzodiazepines are the most difficult to discontinue; weeks or months may be required, with very gradual dosage decrements, to accomplish their complete outpatient removal.

Because of the heterogeneity of epilepsy, complete discontinuance of antiseizure drug administration is an especially difficult problem. If a patient is seizure-free for 3 or 4 years, a trial of gradual discontinuance is often warranted.

OVERDOSE

Antiseizure drugs are central nervous system depressants but are rarely lethal. Very high blood levels are usually necessary before overdoses can be considered life-threatening. The most dangerous effect of antiseizure drugs after large overdoses is respiratory depression, which may be potentiated by other agents, such as alcohol. Treatment of antiseizure drug overdose is supportive; stimulants should not be used. Efforts to hasten removal of antiseizure drugs, such as alkalinization of the urine (phenytoin is a weak acid), are usually ineffective.

SUICIDALITY

An FDA analysis of suicidal behavior during clinical trials of antiseizure drugs was carried out in 2008. The presence of either suicidal behavior or suicidal ideation was 0.37% in patients taking active drugs and 0.24% in patients taking placebo. This, according to one analyst, represents an additional 2 of 1000 patients with such thoughts or behaviors. It is noteworthy that, although the entire class may receive some changes in labeling, the odds ratios for carbamazepine and for valproate were less than 1, and no data were available for phenytoin. Whether this effect is real or inextricably associated with this serious, debilitating disorder—with its inherently high rate of suicidality—is unclear.

SUMMARY Antiseizure Drugs

Subclass	Mechanism of Action	Pharmacokinetics	Clinical Applications	Toxicities, Interactions
CYCLIC UREIDES				
• Phenytoin, fosphenytoin	Block high-frequency firing of neurons through action on voltage-gated (VG) Na^+ channels • decreases synaptic release of glutamate	Absorption is formulation dependent • highly bound to plasma proteins • no active metabolites • dose-dependent elimination, $t_{1/2}$ 12–36 h • fosphenytoin is for IV, IM routes	Generalized tonic-clonic seizures, partial seizures	*Toxicity:* Diplopia, ataxia, gingival hyperplasia, hirsutism, neuropathy • *Interactions:* Phenobarbital, carbamazepine, isoniazid, felbamate, oxcarbazepine, topiramate, fluoxetine, fluconazole, digoxin, quinidine, cyclosporine, steroids, oral contraceptives, others
• Primidone	Similar to phenytoin but converted to phenobarbital	Well absorbed orally • not highly bound to plasma proteins • peak concentrations in 2–6 h • $t_{1/2}$ 10–25 h • two active metabolites (phenobarbital and phenylethylmalonamide)	Generalized tonic-clonic seizures, partial seizures	*Toxicity:* Sedation, cognitive issues, ataxia, hyperactivity • *Interactions:* Similar to phenobarbital
• Phenobarbital	Enhances phasic $GABA_A$ receptor responses • reduces excitatory synaptic responses	Nearly complete absorption • not significantly bound to plasma proteins • peak concentrations in 0.5–4 h • no active metabolites • $t_{1/2}$ varies from 75 to 125 h	Generalized tonic-clonic seizures, partial seizures, myoclonic seizures, generalized seizures, neonatal seizures, status epilepticus	*Toxicity:* Sedation, cognitive issues, ataxia, hyperactivity • *Interactions:* Valproate, carbamazepine, felbamate, phenytoin, cyclosporine, felodipine, lamotrigine, nifedipine, nimodipine, steroids, theophylline, verapamil, others
• Ethosuximide	Reduces low-threshold Ca^{2+} currents (T-type)	Well absorbed orally, with peak levels in 3–7 h • not protein-bound • completely metabolized to inactive compounds • $t_{1/2}$ typically 40 h	Absence seizures	*Toxicity:* Nausea, headache, dizziness, hyperactivity • *Interactions:* Valproate, phenobarbital, phenytoin, carbamazepine, rifampicin
TRICYCLICS				
• Carbamazepine	Blocks high-frequency firing of neurons through action on VG Na^+ channels • decreases synaptic release of glutamate	Well absorbed orally, with peak levels in 6–8 h • no significant protein binding • metabolized in part to active 10-11-epoxide • $t_{1/2}$ of parent ranges from 8 to 12 h in treated patients to 36 h in normal subjects	Generalized tonic-clonic seizures, partial seizures	*Toxicity:* Nausea, diplopia, ataxia, hyponatremia, headache • *Interactions:* Phenytoin, carbamazepine, valproate, fluoxetine, verapamil, macrolide antibiotics, isoniazid, propoxyphene, danazol, phenobarbital, primidone, many others
• *Oxcarbazepine: Similar to carbamazepine; shorter half-life but active metabolite with longer duration and fewer interactions reported*				
• *Eslicarbazepine acetate: Similar to oxcarbazepine but shown to be effective when given once daily and may be more rapidly converted to the active metabolite*				
BENZODIAZEPINES				
• Diazepam	Potentiates $GABA_A$ responses	Well absorbed orally • rectal administration gives peak concentration in ~1 h with 90% bioavailability • IV for status epilepticus • highly protein-bound • extensively metabolized to several active metabolites • $t_{1/2}$ ~2 d	Status epilepticus, seizure clusters	*Toxicity:* Sedation • *Interactions:* Minimal
• Clonazepam	As for diazepam	>80% bioavailability • extensively metabolized but no active metabolites • $t_{1/2}$ 20–50 h	Absence seizures, myoclonic seizures, infantile spasms	*Toxicity:* Similar to diazepam • *Interactions:* Minimal
• *Lorazepam: Similar to diazepam*				
• *Clobazam: Indications include absence seizures, myoclonic seizures, infantile spasms*				

(*continued*)

Subclass	Mechanism of Action	Pharmacokinetics	Clinical Applications	Toxicities, Interactions
GABA DERIVATIVES				
• Gabapentin	Decreases excitatory transmission by acting on VG Ca^{2+} channels presynaptically ($\alpha_2\delta$ subunit)	Bioavailability 50%, decreasing with increasing doses • not bound to plasma proteins • not metabolized • $t_{1/2}$ 6–8 h	Generalized tonic-clonic seizures, partial seizures, generalized seizures	*Toxicity:* Somnolence, dizziness, ataxia • *Interactions:* Minimal
• Pregabalin	As for gabapentin	Well absorbed orally • not bound to plasma proteins • not metabolized • $t_{1/2}$ 6–7 h	Partial seizures	*Toxicity:* Somnolence, dizziness, ataxia • *Interactions:* Minimal
• Vigabatrin	Irreversibly inhibits GABA-transaminase	70% bioavailable • not bound to plasma proteins • not metabolized, • $t_{1/2}$ 5–7 h (not relevant because of mechanism of action)	Partial seizures, infantile spasms	*Toxicity:* Drowsiness, dizziness, psychosis, visual field loss • *Interactions:* Minimal
OTHER				
• Valproate	Blocks high-frequency firing of neurons • modifies amino acid metabolism	Well absorbed from several formulations • highly bound to plasma proteins • extensively metabolized • $t_{1/2}$ 9–16 h	Generalized tonic-clonic seizures, partial seizures, generalized seizures, absence seizures, myoclonic seizures	*Toxicity:* Nausea, tremor, weight gain, hair loss, teratogenic, hepatotoxic • *Interactions:* Phenobarbital, phenytoin, carbamazepine, lamotrigine, felbamate, rifampin, ethosuximide, primidone
• Lamotrigine	Prolongs inactivation of VG Na^+ channels • acts presynaptically on VG Ca^{2+} channels, decreasing glutamate release	Well absorbed orally • no significant protein binding • extensively metabolized, but no active metabolites • $t_{1/2}$ 25–35 h	Generalized tonic-clonic seizures, generalized seizures, partial seizures, absence seizures	*Toxicity:* Dizziness, headache, diplopia, rash • *Interactions:* Valproate, carbamazepine, oxcarbazepine, phenytoin, phenobarbital, primidone, succinimides, sertraline, topiramate
• Levetiracetam	Action on synaptic protein SV_2A	Well absorbed orally • not bound to plasma proteins • metabolized to 3 inactive metabolites • $t_{1/2}$ 6–11 h	Generalized tonic-clonic seizures, partial seizures, generalized seizures	*Toxicity:* Nervousness, dizziness, depression, seizures • *Interactions:* Rare
• Retigabine	Enhances K^+ channel opening	Readily absorbed • requires 3-times daily dosing	Adjunctive treatment of partial seizures	*Toxicity:* Dizziness, somnolence, confusion, blurred vision • *Interactions:* minimal
• Rufinamide	Prolongs inactivation of VG Na^+ channels	Well absorbed orally • peak concentrations in 4–6 h • $t_{1/2}$ 6–10 h • minimal plasma protein binding • no active metabolites • mostly excreted in urine	Adjunctive treatment of the Lennox-Gastaut syndrome	*Toxicity:* Somnolence, vomiting, pyrexia, diarrhea • *Interactions:* Not metabolized via P450 enzymes, but antiseizure drug interactions may be present
• Tiagabine	Blocks GABA reuptake in forebrain by selective blockade of GAT-1	Well absorbed • highly bound to plasma proteins • extensively metabolized, but no active metabolites • $t_{1/2}$ 4–8 h	Partial seizures	*Toxicity:* Nervousness, dizziness, depression, seizures • *Interactions:* Phenobarbital, phenytoin, carbamazepine, primidone
• Topiramate	Multiple actions on synaptic function, probably via actions on phosphorylation	Well absorbed • not bound to plasma proteins • extensively metabolized, but 40% excreted unchanged in the urine • no active metabolites • $t_{1/2}$ 20 h, but decreases with concomitant drugs	Generalized tonic-clonic seizures, partial seizures, generalized seizures, absence seizures, migraine	*Toxicity:* Somnolence, cognitive slowing, confusion, paresthesias • *Interactions:* Phenytoin, carbamazepine, oral contraceptives, lamotrigine, lithium?
• Zonisamide	Blocks high-frequency firing via action on VG Na^+ channels	Approximately 70% bioavailable orally • minimally bound to plasma proteins • >50% metabolized • $t_{1/2}$ 50–70 h	Generalized tonic-clonic seizures, partial seizures, myoclonic seizures	*Toxicity:* Drowsiness, cognitive impairment, confusion, poor concentration • *Interactions:* Minimal
• Lacosamide	Enhances slow inactivation of Na^+ channels • blocks effect of neurotrophins (via CRMP-2)	Well absorbed • minimal protein binding • one major nonactive metabolite • $t_{1/2}$ 12–14 h	Generalized tonic-clonic seizures, partial seizures	*Toxicity:* Dizziness, headache, nausea • small increase in PR interval • *Interactions:* Minimal

PREPARATIONS AVAILABLE

Carbamazepine (generic, Tegretol)
Oral: 200 mg tablets; 100 mg chewable tablets; 100 mg/5 mL suspension
Oral extended-release: 100, 200, 400 mg tablets; 200, 300 mg capsules

Clonazepam (generic, Klonopin)
Oral: 0.5, 1, 2 mg tablets

Clorazepate dipotassium (generic, Tranxene)
Oral: 3.75, 7.5, 15 mg tablets, capsules
Oral sustained-release (Tranxene-SD): 11.25, 22.5 mg tablets

Diazepam (generic, Valium, others)
Oral: 2, 5, 10 mg tablets; 5 mg/5 mL, 5 mg/mL solutions
Parenteral: 5 mg/mL for IV injection
Rectal: 2.5, 5, 10, 15, 20 mg viscous rectal solution

Eslicarbazepine (Stedesa)
Oral: 400 mg tablets

Ethosuximide (generic, Zarontin)
Oral: 250 mg capsules; 250 mg/5 mL syrup

Ethotoin (Peganone)
Oral: 250, 500 mg tablets

Felbamate (Felbatol)
Oral: 400, 600 mg tablets; 600 mg/5 mL suspension

Fosphenytoin (Cerebyx)
Parenteral: 75 mg/mL for IV or IM injection

Gabapentin (Neurontin)
Oral: 100, 300, 400 mg capsules; 600, 800 mg filmtabs; 50 mg/mL solution

Lacosamide (Vimpat)
Oral: 50, 100, 150, 200, 300 mg tablets, 15 mg/mL solution
Parenteral: 10 mg/mL for IV injection

Lamotrigine (generic, Lamictal)
Oral: 25, 100, 150, 200 mg tablets; 2, 5, 25 mg chewable tablets

Levetiracetam (generic, Keppra)
Oral: 250, 500, 750, 1000 mg tablets, 100 mg/mL solution
Parenteral: 100 mg/mL for injection

Lorazepam (generic, Ativan)
Oral: 0.5, 1, 2 mg tablets; 2 mg/mL solution
Parenteral: 2, 4 mg/mL for IV or IM injection

Mephenytoin (Mesantoin)
Oral: 100 mg tablets

Mephobarbital (Mebaral)
Oral: 32, 50, 100 mg tablets

Methsuximide (Celontin)
Oral: 150, 300 mg capsules

Oxcarbazepine (Trileptal)
Oral: 100, 300, 600 mg tablets; 60 mg/mL suspension

Pentobarbital sodium (generic, Nembutal)
Parenteral: 50 mg/mL for IV or IM injection

Phenobarbital (generic, Luminal Sodium, others)
Oral: 15, 16, 30, 60, 90, 100 mg tablets; 16 mg capsules; 15, 20 mg/5 mL elixirs
Parenteral: 30, 60, 65, 130 mg/mL for IV or IM injection

Phenytoin (generic, Dilantin, others)
Oral (prompt release): 100 mg capsules; 50 mg chewable tablets; 125 mg/5 mL suspension
Oral extended action: 30, 100 mg capsules
Oral slow release (Phenytek): 200, 300 mg capsules
Parenteral: 50 mg/mL for IV injection

Pregabalin (Lyrica)
Oral: 25, 50, 75, 100, 150, 200, 300 mg capsules

Primidone (generic, Mysoline)
Oral: 50, 250 mg tablets; 250 mg/5 mL suspension

Retigabine (Trobalt in Europe; ezogabine, Potiga in the USA)

Rufinamide (Banzel)
Oral: 200, 400 mg tablets

Stiripentol (Diacomit)
Oral: 250, 500 mg capsules

Tiagabine (Gabitril)
Oral: 2, 4, 12, 16, 20 mg tablets

Topiramate (Topamax)
Oral: 25, 50, 100, 200 mg tablets; 15, 25 mg sprinkle capsules

Trimethadione (Tridione)
Oral: 150 mg chewable tablets; 300 mg capsules; 40 mg/mL solution

Valproic acid (generic, Depakene)
Oral: 250 mg capsules; 250 mg/5 mL syrup (sodium valproate)
Oral sustained-release (Depakote): 125, 250, 500 mg tablets (as divalproex sodium)
Parenteral (Depacon): 100 mg/mL in 5 mL vial for IV injection

Vigabatrin (Sabril)
Oral: 500 mg tablets; 500 mg powder for solution

Zonisamide (generic, Zonegran)
Oral: 25, 50, 100 mg tablets

REFERENCES

Arroyo S: Rufinamide. Neurotherapeutics 2007;4:155.

Avorn J: Drug warnings that can cause fits—communicating risks in a data-poor environment. N Engl J Med 2008;359:991.

Bialer M: Progress report on new antiepileptic drugs: A summary of the tenth EILAT conference (EILAT X). Epilepsy Res 2010;92:89.

Brodie MJ et al: Rufinamide for the adjunctive treatment of partial seizures in adults and adolescents: A randomized placebo-controlled trial. Epilepsia 2009;50:1899.

Cross SA, Curran MP: Lacosamide in partial onset seizures. Drugs 2009;69:449.

Ettinger AB, Argoff CE: Use of antiepileptic drugs for non-epileptic conditions: Psychiatric disorders and chronic pain. Neurotherapeutics 2007;4:75.

Faught, E. Ezogabine: A new angle on potassium gates. Epilepsy Currents, 2011; 11:75.

French JA et al: Historical control monotherapy design in the treatment of epilepsy. Epilepsia 2010:51:1936.

Glauser TA et al: Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. N Engl J Med 2010;362:790.

Kaminski RM et al: SV2A is a broad-spectrum anticonvulsant target: Functional correlation between protein binding and seizure protection in models of both partial and generalized epilepsy. Neuropharmacol 2008;54:715.

Kobayashi T et al: Inhibitory effects of the antiepileptic drug ethosuximide on G-protein-activated inwardly rectifying K+ channels. Neuropharmacol 2009;56:499.

Meldrum BS, Rogawski MA: Molecular targets for antiepileptic drug development. Neurotherapeutics 2007;4:18.

Molgaard-Nielsen D, Hviid A: Newer-generation antiepileptic drugs and the risk of major birth defects. JAMA 2011;305:1996

Porter RJ et al: Clinical development of drugs for epilepsy: A review of approaches in the United States and Europe. Epilepsy Research 2010;89:163.

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CHAPTER 25

General Anesthetics

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CASE STUDY

An elderly man with type 2 diabetes mellitus and ischemic pain in the lower extremity is scheduled for femoral-to-popliteal bypass surgery. He has a history of hypertension and coronary artery disease with symptoms of stable angina and can walk only half a block before pain in his legs forces him to stop. He has a 50 pack-year smoking history but stopped 2 years ago. His medications include atenolol, atorvastatin, and hydrochlorothiazide. The nurse in the preoperative holding area obtains the following vital signs: temperature 36.8°C (98.2°F), blood pressure 168/100 mm Hg, heart rate 78 bpm, oxygen saturation by pulse oximeter 96% while breathing room air, pain 5/10 in the right lower leg. What anesthetic agents will you choose and why? Does the choice of anesthetic make a difference?

For centuries, humankind has relied on natural medicines and physical methods to control surgical pain. Historical texts describe the sedative effects of cannabis, henbane, mandrake, and opium poppy. Physical methods such as cold, nerve compression, carotid artery occlusion, and cerebral concussion were also employed, with variable effect. Although surgery was performed under ether anesthesia as early as 1842, the first public demonstration of surgical general anesthesia in 1846 is usually considered to be the start of a new era of anesthesia. For the first time physicians had a reliable means to keep their patients from experiencing pain during surgical procedures.

The neurophysiologic state produced by general anesthetics is characterized by five primary effects: **unconsciousness, amnesia, analgesia, inhibition of autonomic reflexes**, and **skeletal muscle relaxation**. None of the currently available anesthetic agents when used alone can achieve all five of these desired effects. In addition, an ideal anesthetic drug should induce rapid, smooth loss of consciousness, be rapidly reversible upon discontinuation, and possess a wide margin of safety.

The modern practice of anesthesiology relies on the use of combinations of intravenous and inhaled drugs (**balanced anesthesia** techniques) to take advantage of the favorable properties of each agent while minimizing their adverse effects. The choice of anesthetic technique is determined by the type of diagnostic, therapeutic, or surgical intervention to be performed. For minor superficial surgery or for invasive diagnostic procedures, oral or parenteral sedatives can be used in combination with local anesthetics, so-called **monitored anesthesia care** techniques (see Box: Sedation & Monitored Anesthesia Care, and Chapter 26). These techniques provide profound analgesia, with retention of the patient's ability to maintain a patent airway and to respond to verbal commands. For more extensive surgical procedures, anesthesia may begin with preoperative benzodiazepines, be induced with an intravenous agent (eg, thiopental or propofol), and be maintained with a combination of inhaled (eg, volatile agents, nitrous oxide) or intravenous (eg, propofol, opioid analgesics) drugs, or both.

MECHANISM OF GENERAL ANESTHETIC ACTION

General anesthetics have been in clinical use for more than 160 years but their mechanism of action remains unknown. Initial research focused on identifying a single biologic site of action for these drugs. In recent years this "unitary theory" of anesthetic action has been supplanted by a more complex picture of molecular targets located at multiple levels of the central nervous system (CNS).

Anesthetics affect neurons at various cellular locations, but the primary focus has been on the synapse. A presynaptic action may alter the release of neurotransmitters, whereas a postsynaptic effect may change the frequency or amplitude of impulses exiting the synapse. At the organ level, the effect of anesthetics may result from

Sedation & Monitored Anesthesia Care

Many diagnostic and minor therapeutic surgical procedures can be performed without general anesthesia using sedation-based anesthetic techniques. In this setting, regional or local anesthesia supplemented with midazolam or propofol and opioid analgesics (or ketamine) may be a more appropriate and safer approach than general anesthesia for superficial surgical procedures. This anesthetic technique is known as monitored anesthesia care, often abbreviated as MAC, not to be confused with the minimal alveolar concentration for the comparison of potencies of inhaled anesthetics (see text and Box: What Does Anesthesia Represent & Where Does It Work?). The technique typically involves the use of intravenous midazolam for premedication (to provide anxiolysis, amnesia, and mild sedation) followed by a titrated, variable-rate propofol infusion (to provide moderate to deep levels of sedation). A potent opioid analgesic or ketamine may be added to minimize the discomfort associated with the injection of local anesthesia and the surgical manipulations.

Another approach, used primarily by nonanesthesiologists, is called **conscious sedation**. This technique refers to drug-induced alleviation of anxiety and pain in combination with an altered level of consciousness associated with the use of smaller doses of sedative medications. In this state the patient retains the ability to maintain a patent airway and is responsive to verbal commands. A wide variety of intravenous anesthetic drugs have proved to be useful drugs in conscious sedation techniques (eg, diazepam, midazolam, propofol). Use of benzodiazepines and opioid analgesics (eg, fentanyl) in conscious sedation protocols has the advantage of being reversible by the specific receptor antagonist drugs (flumazenil and naloxone, respectively).

A specialized form of sedation is occasionally required in the ICU, when patients are under severe stress and require mechanical ventilation for prolonged periods. In this situation, sedative-hypnotic drugs and low doses of intravenous anesthetics may be combined. Recently, dexmedetomidine has become a popular choice for this indication.

Deep sedation is similar to a light state of general (intravenous) anesthesia involving decreased consciousness from which the patient is not easily aroused. The transition from deep sedation to general anesthesia is fluid, and it is sometimes difficult to clearly determine where the transition is. Because deep sedation is often accompanied by a loss of protective reflexes, an inability to maintain a patent airway, and lack of verbal responsiveness to surgical stimuli, this state may be indistinguishable from intravenous anesthesia. Intravenous agents used in deep sedation protocols mainly include the sedative-hypnotics propofol and midazolam, sometimes in combination with potent opioid analgesics or ketamine, depending on the level of pain associated with the surgery or procedure.

strengthening inhibition or from diminishing excitation within the CNS. Studies on isolated spinal cord tissue have demonstrated that excitatory transmission is impaired more strongly by anesthetics than inhibitory effects are potentiated.

Chloride channels (γ-aminobutyric acid-A [$GABA_A$] and glycine receptors) and potassium channels (K_{2P}, possibly K_v, and K_{ATP} channels) remain the primary *inhibitory* ion channels considered legitimate candidates of anesthetic action. *Excitatory* ion channel targets include those activated by acetylcholine (nicotinic and muscarinic receptors), by excitatory amino acids (amino-3-hydroxy-5-methyl-4-isoxazol-propionic acid [AMPA], kainate, and *N*-methyl-D-aspartate [NMDA] receptors), or by serotonin ($5\text{-}HT_2$ and $5\text{-}HT_3$ receptors). Figure 25–1 depicts the relation of these inhibitory and excitatory targets of anesthetics within the context of the nerve terminal.

INHALED ANESTHETICS

A clear distinction should be made between volatile and gaseous anesthetics, both of which are administered by inhalation. Volatile anesthetics (halothane, enflurane, isoflurane, desflurane, sevoflurane) have low vapor pressures and thus high boiling points so that they are liquids at room temperature (20°C) and sea-level ambient pressure, whereas gaseous anesthetics (nitrous oxide, xenon) have high vapor pressures and low boiling points such that they are in gas form at room temperature. Figure 25–2 shows the chemical structures of important, clinically used, inhaled anesthetics.

PHARMACOKINETICS

Inhaled anesthetics, volatile as well as gaseous, are taken up through gas exchange in the alveoli. Uptake from the alveoli into the blood and distribution and partitioning into the effect compartments are important determinants of the kinetics of these agents. As previously mentioned, an ideal anesthetic should have a rapid onset (induction), and its effect should be rapidly terminated. To achieve this, the effect site concentration in the CNS (brain and spinal cord) will need to change rapidly. Several factors determine how quickly the CNS concentration changes.

Uptake & Distribution

A. Inspired Concentration and Ventilation

The driving force for uptake of an inhaled anesthetic is the alveolar concentration. Two parameters that can be controlled by the anesthesiologist determine how quickly the alveolar concentration changes: (1) *inspired concentration* or *partial pressure,* and (2) *alveolar ventilation.* The partial pressure of an inhaled anesthetic in the inspired gas mixture directly affects the maximum partial pressure that can be achieved in the alveoli and the rate of increase of

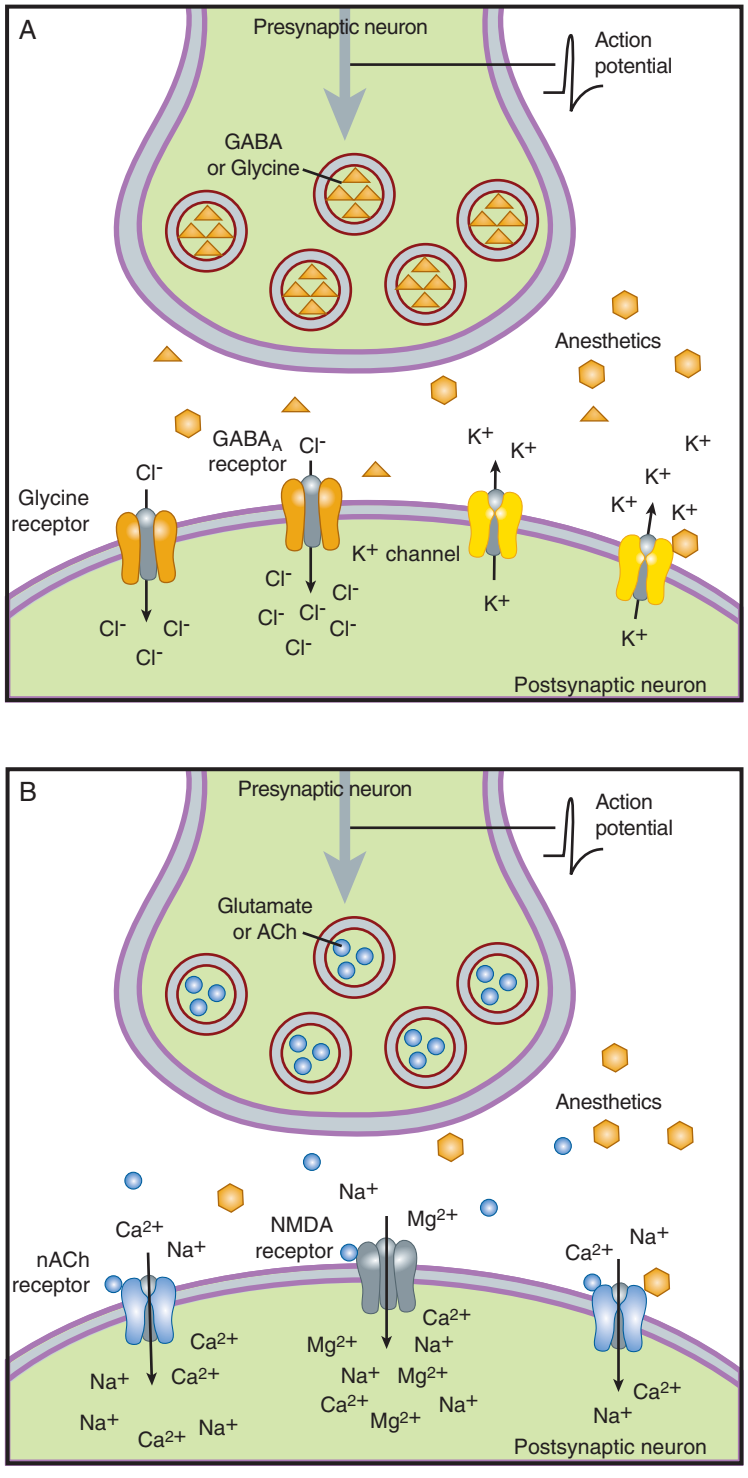

FIGURE 25–1 Putative targets of anesthetic action. Anesthetic drugs may increase inhibitory synaptic activity or diminish excitatory activity. ACh, acetylcholine; $GABA_A$, γ-aminobutyric acid-A.

the partial pressure in the alveoli and, ultimately, the blood. Increases in the inspired partial pressure increase the rate of rise in the alveoli and thus accelerate induction. The increase of partial pressure in the alveoli is usually expressed as a ratio of alveolar concentration (F_A) over inspired concentration (F_I); the faster F_A/F_I approaches 1 (1 representing the equilibrium), the faster anesthesia will occur during an inhaled induction.

The other parameter that directly controls the rate by which F_A/F_I approaches 1 is alveolar ventilation. An increase in ventilation will increase the rate of rise. The magnitude of the effect varies

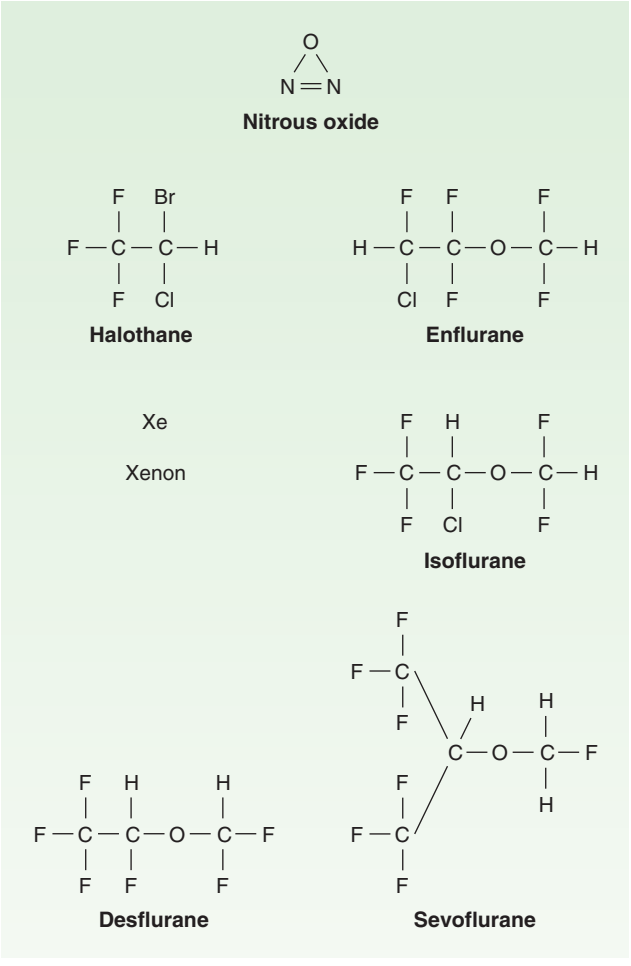

FIGURE 25–2 Chemical structures of inhaled anesthetics.

according to the blood:gas partition coefficient. An increase in pulmonary ventilation is accompanied by only a slight increase in arterial tension of an anesthetic with low blood solubility, but can significantly increase tension of agents with moderate to high blood solubility (Figure 25–3). For example, a fourfold increase in the ventilation rate almost doubles the F_A/F_I ratio for halothane during the first 10 minutes of administration but increases the F_A/F_I ratio for nitrous oxide by only 15%. Thus, hyperventilation increases the speed of induction of anesthesia with inhaled anesthetics that would normally have a slow onset. Depression of respiration by opioid analgesics slows the onset of anesthesia of inhaled anesthetics unless ventilation is manually or mechanically assisted.

B. Factors Controlling Uptake

The increase of F_A/F_I, which is an important determinant of the speed of induction, is opposed by the uptake of anesthetic into the blood, which is determined by pharmacokinetic parameters unique to the anesthetic agent as well as patient factors.

1. Solubility—One of the most important factors influencing the transfer of an anesthetic from the lungs to the arterial blood is its solubility characteristics (Table 25–1). The blood:gas partition coefficient is a useful index of solubility and defines the relative affinity of an anesthetic for the blood compared with that of inspired gas. The partition coefficients for desflurane and nitrous oxide, which are relatively insoluble in blood, are extremely low. When an anesthetic with low blood solubility diffuses from the lung into the arterial blood, relatively few molecules are required to raise its partial pressure; therefore, the arterial tension rises rapidly (Figure 25–4, top; nitrous oxide, desflurane, sevoflurane). Conversely, for anesthetics with moderate to high solubility (Figure 25–4, bottom; halothane, isoflurane), more molecules

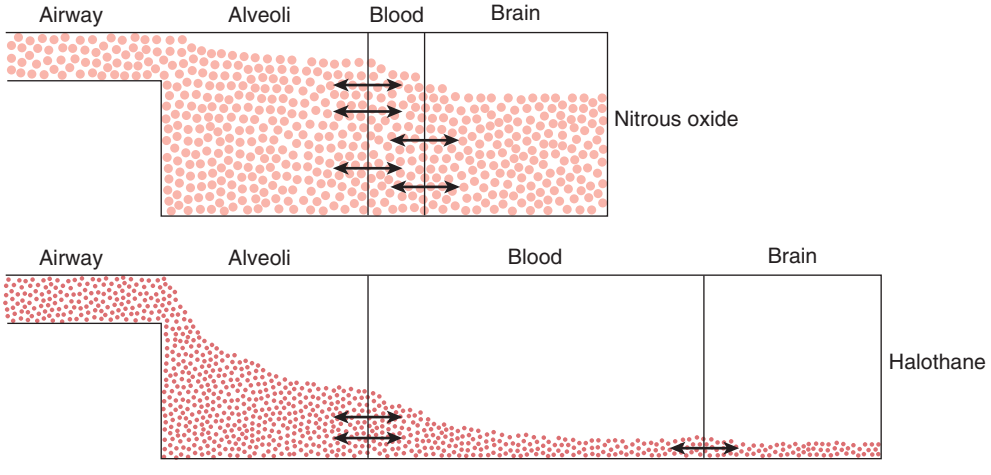

FIGURE 25–3 Why induction of anesthesia is slower with more soluble anesthetic gases. In this schematic diagram, solubility in blood is represented by the relative size of the blood compartment (the more soluble, the larger the compartment). Relative partial pressures of the agents in the compartments are indicated by the degree of filling of each compartment. For a given concentration or partial pressure of the two anesthetic gases in the inspired air, it will take much longer for the blood partial pressure of the more soluble gas (halothane) to rise to the same partial pressure as in the alveoli. Since the concentration of the anesthetic agent in the brain can rise no faster than the concentration in the blood, the onset of anesthesia will be slower with halothane than with nitrous oxide.

TABLE 25–1 Pharmacologic properties of inhaled anesthetics.

Anesthetic	Blood:Gas Partition Coefficient[1]	Brain:Blood Partition Coefficient[1]	Minimal Alveolar Concentration (MAC) (%)[2]	Metabolism	Comments
Nitrous oxide	0.47	1.1	> 100	None	Incomplete anesthetic; rapid onset and recovery
Desflurane	0.42	1.3	6–7	< 0.05%	Low volatility; poor induction agent (pungent); rapid recovery
Sevoflurane	0.69	1.7	2.0	2–5% (fluoride)	Rapid onset and recovery; unstable in soda-lime
Isoflurane	1.40	2.6	1.40	< 2%	Medium rate of onset and recovery
Enflurane	1.80	1.4	1.7	8%	Medium rate of onset and recovery
Halothane	2.30	2.9	0.75	> 40%	Medium rate of onset and recovery

[1] Partition coefficients (at 37°C) are from multiple literature sources.

[2] MAC is the anesthetic concentration that produces immobility in 50% of patients exposed to a noxious stimulus.

dissolve before partial pressure changes significantly, and arterial tension of the gas increases less rapidly. A blood:gas partition coefficient of 0.47 for nitrous oxide means that at equilibrium, the concentration in blood is 0.47 times the concentration in the alveolar space (gas). A larger blood:gas partition coefficient produces a greater uptake of anesthetic and therefore reduces the time required for F_A/F_I to approach 1 (equilibrium, Figure 25–4).

2. Cardiac output—Changes in pulmonary blood flow have obvious effects on the uptake of anesthetic gases from the alveolar space. An increase in pulmonary blood flow (ie, increased cardiac output) will increase the uptake of anesthetic, thereby decreasing the rate by which F_A/F_I rises, which will decrease the rate of induction of anesthesia. To better understand this mechanism, one should think about the effect of cardiac output in combination with the tissue distribution and uptake of anesthetic into other tissue compartments. An increase in cardiac output and pulmonary blood flow will increase uptake of anesthetic into the blood, but the anesthetic taken up will be distributed in all tissues, not just the CNS. Cerebral blood flow is well regulated and the increased cardiac output will therefore increase delivery of anesthetic to other tissues and not the brain.

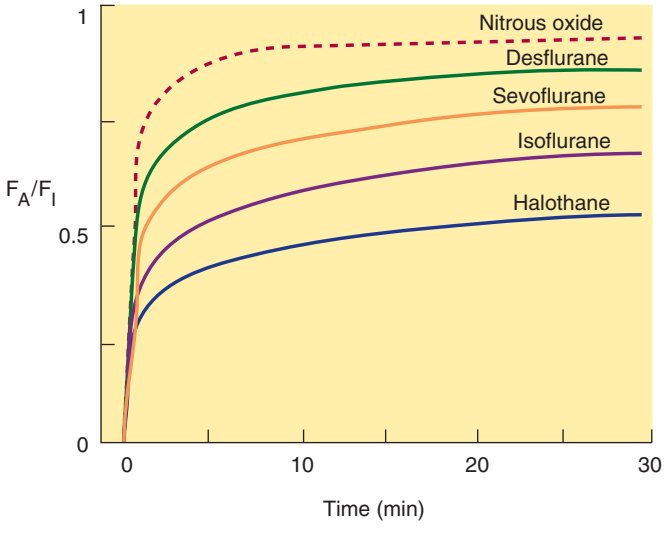

FIGURE 25–4 The alveolar anesthetic concentration (F_A) approaches the inspired anesthetic concentration (F_I) fastest for the least soluble agents.

3. Alveolar-venous partial pressure difference—The anesthetic partial pressure difference between alveolar and mixed venous blood is dependent mainly on uptake of the anesthetic by the tissues, including nonneural tissues. Depending on the rate and extent of tissue uptake, venous blood returning to the lungs may contain significantly less anesthetic than arterial blood. The greater this difference in anesthetic gas tensions, the more time it will take to achieve equilibrium with brain tissue. Anesthetic uptake into tissues is influenced by factors similar to those that determine transfer of the anesthetic from the lung to the intravascular space, including tissue:blood partition coefficients, rates of blood flow to the tissues, and concentration gradients.

During the induction phase of anesthesia (and the initial phase of the maintenance period), the tissues that exert greatest influence on the arteriovenous anesthetic concentration gradient are those that are highly perfused (eg, brain, heart, liver, kidneys, and splanchnic bed). Combined, these tissues receive over 75% of the resting cardiac output. In the case of volatile anesthetics with relatively high solubility in highly perfused tissues, venous blood concentration initially is very low, and equilibrium with the alveolar space is achieved slowly.

During maintenance of anesthesia with inhaled anesthetics, the drug continues to be transferred between various tissues at rates dependent on the solubility of the agent, the concentration gradient between the blood and the tissue, and the tissue blood flow. Although muscle and skin constitute 50% of the total body mass, anesthetics accumulate more slowly in these tissues than in highly perfused tissues (eg, brain) because they receive only one fifth of the resting cardiac output. Although most anesthetic agents are highly soluble in adipose (fatty) tissues, the relatively low blood

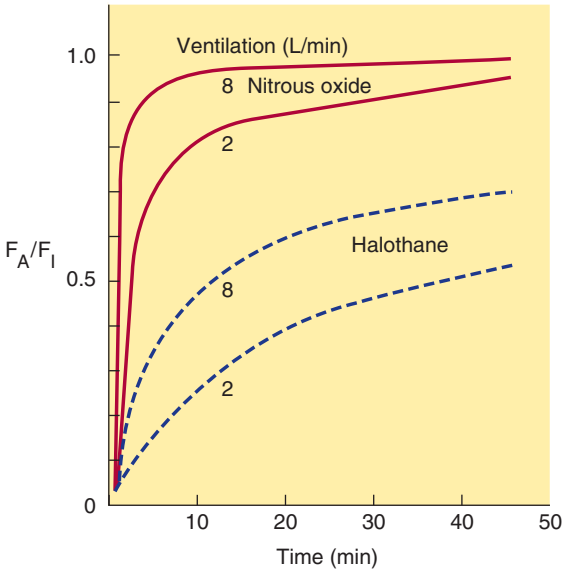

FIGURE 25–5 Effect of ventilation on F_A/F_I. Increased ventilation (8 versus 2 L/min) has a much greater effect on equilibration of halothane than nitrous oxide.

perfusion to these tissues delays accumulation, and equilibrium is unlikely to occur with most anesthetics during a typical 1- to 3-hour operation.

The combined effect of ventilation, solubility in the different tissues, cardiac output, and blood flow distribution determines the rate of rise of F_A/F_I characteristic of each drug (Figure 25–5). When inducing anesthesia by inhalation only, the rate by which F_A/F_I approaches 1 will determine the speed of induction.

Elimination

Recovery from inhalation anesthesia follows some of the same principles in reverse that are important during induction. The time to recovery from inhalation anesthesia depends on the rate of elimination of the anesthetic from the brain. One of the most important factors governing rate of recovery is the blood:gas partition coefficient of the anesthetic agent. Other factors controlling rate of recovery include pulmonary blood flow, magnitude of ventilation, and tissue solubility of the anesthetic. Two features differentiate the recovery phase from the induction phase. First, transfer of an anesthetic from the lungs to blood can be enhanced by increasing its concentration in inspired air, but the reverse transfer process cannot be enhanced because the concentration in the lungs cannot be reduced below zero. Second, at the beginning of the recovery phase, the anesthetic gas tension in different tissues may be quite variable, depending on the specific agent and the duration of anesthesia. In contrast, at the start of induction of anesthesia the initial anesthetic tension is zero in all tissues.

Inhaled anesthetics that are relatively insoluble in blood (ie, possess low blood:gas partition coefficients) and brain are eliminated at faster rates than the more soluble anesthetics. The washout of nitrous oxide, desflurane, and sevoflurane occurs at a rapid rate, leading to a more rapid recovery from their anesthetic effects compared with halothane and isoflurane. Halothane is approximately twice as soluble in brain tissue and five times more soluble in blood than nitrous oxide and desflurane; its elimination therefore takes place more slowly, and recovery from halothane- and isoflurane-based anesthesia is predictably less rapid.

The duration of exposure to the anesthetic can also have a significant effect on the recovery time, especially in the case of the more soluble anesthetics (eg, halothane and isoflurane). Accumulation of anesthetics in muscle, skin, and fat increases with prolonged exposure (especially in obese patients), and blood tension may decline slowly during recovery as the anesthetic is slowly eliminated from these tissues. Although recovery may be rapid even with the more soluble agents following a short period of exposure, recovery is slow after prolonged administration of halothane or isoflurane.

A. Ventilation

Two parameters that can be manipulated by the anesthesiologist are useful in controlling the speed of induction of and recovery from inhaled anesthesia: (1) concentration of anesthetic in the inspired gas and (2) alveolar ventilation. Because the concentration of anesthetic in the inspired gas cannot be reduced below zero, ventilation is the only way to speed recovery.

B. Metabolism

Modern inhaled anesthetics are eliminated mainly by ventilation and are only metabolized to a very small extent; thus, metabolism of these drugs does not play a significant role in the termination of their effect. However, metabolism may have important implications for their toxicity (see Toxicity of Anesthetic Agents). Hepatic metabolism may also contribute to the elimination of and recovery from some older volatile anesthetics. For example, halothane is eliminated more rapidly during recovery than enflurane, which would not be predicted from their respective tissue solubility. This increased elimination occurs because over 40% of inspired halothane is metabolized during an average anesthetic procedure, whereas less than 10% of enflurane is metabolized over the same period.

In terms of the extent of hepatic metabolism, the rank order for the inhaled anesthetics is halothane > enflurane > sevoflurane > isoflurane > desflurane > nitrous oxide (Table 25–1). Nitrous oxide is not metabolized by human tissues. However, bacteria in the gastrointestinal tract may be able to break down the nitrous oxide molecule.

PHARMACODYNAMICS

Organ System Effects of Inhaled Anesthetics

A. Cerebral Effects

Anesthetic potency is currently described by the minimal alveolar concentration (MAC) required to prevent a response to a surgical

What Does Anesthesia Represent & Where Does It Work?

Anesthetic action has three principal components: immobility, amnesia, and unconsciousness.

Immobility

Immobility is the easiest anesthetic end point to measure. Edmond Eger and colleagues introduced the concept of minimal alveolar concentration (MAC) to quantify the potency of an inhalational anesthetic. They defined 1.0 MAC as the partial pressure of an inhalational anesthetic in the alveoli of the lungs at which 50% of a population of nonrelaxed patients remained immobile at the time of a skin incision. Anesthetic immobility is mediated primarily by neural inhibition within the spinal cord.

Amnesia

The ablation of memory arises from several locations in the CNS, including the hippocampus, amygdala, prefrontal cortex, and regions of the sensory and motor cortices. Memory researchers differentiate two types of memory: (1) explicit memory, ie, specific awareness or consciousness under anesthesia, and (2) implicit memory, the unconscious acquisition of information under adequate levels of anesthesia. Their studies have found that formation of both types of memory is reliably prevented at low MAC values (0.2–0.4 MAC). Prevention of explicit memory (awareness) has spurred the development of monitors such as the bispectral index, electroencephalogram, and entropy monitor of auditory evoked potentials to recognize inadequate planes of anesthesia.

Consciousness

The ability of anesthetic drugs to abolish consciousness requires action at anatomic locations responsible for the formation of human consciousness. Leading neuroscientists studying consciousness identify three regions in the brain involved in generating personal awareness: the cerebral cortex, the thalamus, and the reticular activating system. These regions seem to interact as a cortical system via identified pathways, producing a state in which humans are awake, aware, and perceiving.

Our current state of understanding supports the following framework: sensory stimuli conducted through the reticular formation of the brainstem into supratentorial signaling loops, connecting the thalamus with various regions of the cortex, are the foundation of consciousness. These neural pathways involved in the development of consciousness are disrupted by anesthetics.

incision (see Box: What Does Anesthesia Represent & Where Does It Work?).

Inhaled anesthetics (like intravenous anesthetics, discussed later) decrease the metabolic activity of the brain. Decreased cerebral metabolic rate (CMR) generally reduces blood flow within the brain. However, volatile anesthetics also cause cerebral vasodilation, which can increase cerebral blood flow. The net effect on cerebral blood flow (increase, decrease, or no change) depends on the concentration of anesthetic delivered. At 0.5 MAC, the reduction in CMR is greater than the vasodilation caused by the anesthetic, so cerebral blood flow is decreased. Conversely, at 1.5 MAC, vasodilation by the anesthetic is greater than the reduction in CMR, so cerebral blood flow is increased. In between, at 1.0 MAC, the effects are balanced and cerebral blood flow is unchanged. An increase in cerebral blood flow is clinically undesirable in patients who have increased intracranial pressure because of brain tumor, intracranial hemorrhage, or head injury. Therefore, administration of high concentrations of volatile anesthetics is undesirable in patients with increased intracranial pressure. Hyperventilation can be used to attenuate this response; decreasing the $PaCO_2$ (the partial pressure of carbon dioxide in arterial blood) through hyperventilation causes cerebral vasoconstriction. If the patient is hyperventilated before the volatile agent is started, the increase in intracranial pressure can be minimized.

Nitrous oxide can increase cerebral blood flow and cause increased intracranial pressure. This effect is most likely caused by activation of the sympathetic nervous system (as described above). Therefore, nitrous oxide may be combined with other agents (intravenous anesthetics) or techniques (hyperventilation) that reduce cerebral blood flow in patients with increased intracranial pressure.

Potent inhaled anesthetics produce a basic pattern of change to brain electrical activity as recorded by standard electroencephalography (EEG). Isoflurane, desflurane, sevoflurane, halothane, and enflurane produce initial activation of the EEG at low doses and then slowing of electrical activity up to doses of 1.0–1.5 MAC. At higher concentrations, EEG suppression increases to the point of electrical silence with isoflurane at 2.0–2.5 MAC. Isolated epileptic-like patterns may also be seen between 1.0 and 2.0 MAC, especially with sevoflurane and enflurane, but frank clinical seizure activity has been observed only with enflurane. Nitrous oxide used alone causes fast electrical oscillations emanating from the frontal cortex at doses associated with analgesia and depressed consciousness.

Traditionally, anesthetic effects on the brain produce four stages or levels of increasing depth of CNS depression (Guedel's signs, derived from observations of the effects of inhaled diethyl ether): **Stage I—analgesia:** The patient initially experiences analgesia without amnesia. Later in stage I, both analgesia and amnesia are produced. **Stage II—excitement:** During this stage, the patient appears delirious, may vocalize but is completely amnesic. Respiration is rapid, and heart rate and blood pressure increase. Duration and severity of this light stage of anesthesia is shortened by rapidly increasing the concentration of the agent. **Stage III—surgical anesthesia:** This stage begins with slowing of

respiration and heart rate and extends to complete cessation of spontaneous respiration (apnea). Four planes of stage III are described based on changes in ocular movements, eye reflexes, and pupil size, indicating increasing depth of anesthesia. **Stage IV—medullary depression:** This deep stage of anesthesia represents severe depression of the CNS, including the vasomotor center in the medulla and respiratory center in the brainstem. Without circulatory and respiratory support, death would rapidly ensue.

B. Cardiovascular Effects

Halothane, enflurane, isoflurane, desflurane, and sevoflurane all depress normal cardiac contractility (halothane and enflurane more so than isoflurane, desflurane, and sevoflurane). As a result, all volatile agents tend to decrease mean arterial pressure in direct proportion to their alveolar concentration. With halothane and enflurane, the reduced arterial pressure is caused primarily by myocardial depression (reduced cardiac output) and there is little change in systemic vascular resistance. In contrast, isoflurane, desflurane, and sevoflurane produce greater vasodilation with minimal effect on cardiac output. These differences may have important implications for patients with heart failure. Because isoflurane, desflurane, and sevoflurane better preserve cardiac output as well as reduce preload (ventricular filling) and afterload (systemic vascular resistance), these agents may be better choices for patients with impaired myocardial function.

Nitrous oxide also depresses myocardial function in a concentration-dependent manner. This depression may be significantly offset by a concomitant activation of the sympathetic nervous system resulting in preservation of cardiac output. Therefore, administration of nitrous oxide in combination with the more potent volatile anesthetics can minimize circulatory depressant effects by both anesthetic-sparing and sympathetic-activating actions.

Because all inhaled anesthetics produce a dose-dependent decrease in arterial blood pressure, activation of autonomic nervous system reflexes may trigger increased heart rate. However, halothane, enflurane, and sevoflurane have little effect on heart rate, probably because they attenuate baroreceptor input into the autonomic nervous system. Desflurane and isoflurane significantly increase heart rate because they cause less depression of the baroreceptor reflex. In addition, desflurane can trigger transient sympathetic activation—with elevated catecholamine levels—to cause marked increases in heart rate and blood pressure during administration of high desflurane concentrations or when desflurane concentrations are changed rapidly.

Inhaled anesthetics tend to reduce myocardial oxygen consumption, which reflects depression of normal cardiac contractility and decreased arterial blood pressure. In addition, inhaled anesthetics produce coronary vasodilation. The net effect of decreased oxygen demand and increased coronary flow (oxygen supply) is improved myocardial oxygenation. However, other factors such as surgical stimulation, intravascular volume status, blood oxygen levels, and withdrawal of perioperative β blockers, may tilt the oxygen supply-demand balance toward myocardial ischemia.

Halothane and, to a lesser extent, other volatile anesthetics sensitize the myocardium to epinephrine and circulating catecholamines. Ventricular arrhythmias may occur when patients under anesthesia with halothane are given sympathomimetic drugs or have high circulating levels of endogenous catecholamines (eg, anxious patients, administration of epinephrine-containing local anesthetics, inadequate intraoperative anesthesia or analgesia, patients with pheochromocytomas). This effect is less marked for isoflurane, sevoflurane, and desflurane.

C. Respiratory Effects

All volatile anesthetics possess varying degrees of bronchodilating properties, an effect of value in patients with active wheezing and in status asthmaticus. However, airway irritation, which may provoke coughing or breath-holding, is induced by the pungency of some volatile anesthetics. The pungency of isoflurane and desflurane makes these agents less suitable for induction of anesthesia in patients with active bronchospasm. These reactions rarely occur with halothane and sevoflurane, which are considered nonpungent. Therefore, the bronchodilating action of halothane and sevoflurane makes them the agents of choice in patients with underlying airway problems. Nitrous oxide is also nonpungent and can facilitate inhalational induction of anesthesia in a patient with bronchospasm.

The control of breathing is significantly affected by inhaled anesthetics. With the exception of nitrous oxide, all inhaled anesthetics in current use cause a dose-dependent decrease in tidal volume and an increase in respiratory rate (rapid shallow breathing pattern). However, the increase in respiratory rate varies among agents and does not fully compensate for the decrease in tidal volume, resulting in a decrease in alveolar ventilation. In addition, all volatile anesthetics are respiratory depressants, as defined by a reduced ventilatory response to increased levels of carbon dioxide in the blood. The degree of ventilatory depression varies among the volatile agents, with isoflurane and enflurane being the most depressant. By this hypoventilation mechanism, all volatile anesthetics increase the resting level of Pa_{CO_2}.

Volatile anesthetics also raise the apneic threshold (Pa_{CO_2} level below which apnea occurs through lack of CO_2-driven respiratory stimulation) and decrease the ventilatory response to hypoxia. In practice, the respiratory depressant effects of anesthetics are overcome by assisting (controlling) ventilation mechanically. The ventilatory depression produced by inhaled anesthetics may be counteracted by surgical stimulation; however, low, subanesthetic concentrations of volatile anesthetic present after surgery in the early recovery period can continue to depress the compensatory increase in ventilation normally caused by hypoxia.

Inhaled anesthetics also depress mucociliary function in the airway. During prolonged exposure to inhaled anesthetics, mucus pooling and plugging may result in atelectasis and the development of postoperative respiratory complications, including hypoxemia and respiratory infections.

D. Renal Effects

Inhaled anesthetics tend to decrease glomerular filtration rate (GFR) and urine flow. Renal blood flow may also be decreased by some agents but filtration fraction is increased, implying that autoregulatory control of efferent arteriole tone helps compensate and limits the reduction in GFR. In general these anesthetic

effects are minor compared with the stress of surgery itself and usually reversible after discontinuation of the anesthetic.

E. Hepatic Effects

Volatile anesthetics cause a concentration-dependent decrease in portal vein blood flow that parallels the decline in cardiac output produced by these agents. However, total hepatic blood flow may be relatively preserved as hepatic artery blood flow to the liver may increase or stay the same. Although transient changes in liver function tests may occur following exposure to volatile anesthetics, persistent elevation in liver enzymes is rare except following repeated exposures to halothane (see Toxicity of Anesthetic Agents).

F. Effects on Uterine Smooth Muscle

Nitrous oxide appears to have little effect on uterine musculature. However, the halogenated anesthetics are potent uterine muscle relaxants and produce this effect in a concentration-dependent fashion. This pharmacologic effect can be helpful when profound uterine relaxation is required for intrauterine fetal manipulation or manual extraction of a retained placenta during delivery. However, it can also lead to increased uterine bleeding.

Toxicity of Anesthetic Agents

A. Acute Toxicity

1. Nephrotoxicity—Metabolism of enflurane and sevoflurane may generate compounds that are potentially nephrotoxic. Although their metabolism can liberate nephrotoxic fluoride ions, significant renal injury has been reported only for enflurane with prolonged exposure. The insolubility and rapid elimination of sevoflurane may prevent toxicity. This drug may be degraded by carbon dioxide absorbents in anesthesia machines to form a nephrotoxic vinyl ether compound termed "compound A" which, in high concentrations, has caused proximal tubular necrosis in rats. Nevertheless, there have been no reports of renal injury in humans receiving sevoflurane anesthesia. Moreover, exposure to sevoflurane does not produce any change in standard markers of renal function.

2. Hematotoxicity—Prolonged exposure to nitrous oxide decreases methionine synthase activity, which theoretically could cause megaloblastic anemia. Megaloblastic bone marrow changes have been observed in patients after 12-hour exposure to 50% nitrous oxide. Chronic exposure of dental personnel to nitrous oxide in inadequately ventilated dental operating suites is a potential occupational hazard.

All inhaled anesthetics can produce some carbon monoxide (CO) from their interaction with strong bases in dry carbon dioxide absorbers. CO binds to hemoglobin with high affinity, reducing oxygen delivery to tissues. Desflurane produces the most CO, and intraoperative formation of CO has been reported. CO production can be avoided simply by using fresh carbon dioxide absorbent and by preventing its complete desiccation.

3. Malignant hyperthermia—Malignant hyperthermia is a heritable genetic disorder of skeletal muscle that occurs in susceptible individuals exposed to volatile anesthetics while undergoing general anesthesia (see Chapter 16 and Table 16–4). The depolarizing muscle relaxant succinylcholine may also trigger malignant hyperthermia. The malignant hyperthermia syndrome consists of muscle rigidity, hyperthermia, rapid onset of tachycardia and hypercapnia, hyperkalemia, and metabolic acidosis following exposure to one or more triggering agents. Malignant hyperthermia is a rare but important cause of anesthetic morbidity and mortality. The specific biochemical abnormality is an increase in free cytosolic calcium concentration in skeletal muscle cells. Treatment includes administration of **dantrolene** (to reduce calcium release from the sarcoplasmic reticulum) and appropriate measures to reduce body temperature and restore electrolyte and acid-base balance (see Chapter 27).

Malignant hyperthermia susceptibility is characterized by genetic heterogeneity, and several predisposing clinical myopathies have been identified. It has been associated with mutations in the gene coding for the skeletal muscle ryanodine receptor (RyR1), the calcium release channel on the sarcoplasmic reticulum, and mutant alleles of the gene encoding the α_1 subunit of the human skeletal muscle L-type voltage-dependent calcium channel. However, the genetic loci identified to date account for less than 50% of malignant hyperthermia-susceptible individuals, and genetic testing cannot definitively determine malignant hyperthermia susceptibility. Currently, the most reliable test to establish susceptibility is the in vitro caffeine-halothane contracture test using skeletal muscle biopsy samples.

4. Hepatotoxicity (halothane hepatitis)—Hepatic dysfunction following surgery and general anesthesia is most likely caused by hypovolemic shock, infection conferred by blood transfusion, or other surgical stresses rather than by volatile anesthetic toxicity. However, a small subset of individuals previously exposed to halothane has developed fulminant hepatic failure. The incidence of severe hepatotoxicity following exposure to halothane is estimated to be in the range of 1 in 20,000–35,000. The mechanisms underlying halothane hepatotoxicity remain unclear, but studies in animals implicate the formation of reactive metabolites that either cause direct hepatocellular damage (eg, free radicals) or initiate immune-mediated responses. Cases of hepatitis following exposure to other volatile anesthetics, including enflurane, isoflurane, and desflurane, have rarely been reported.

B. Chronic Toxicity

1. Mutagenicity, teratogenicity, and reproductive effects—Under normal conditions, inhaled anesthetics including nitrous oxide are neither mutagens nor carcinogens in patients. Nitrous oxide can be directly teratogenic in animals under conditions of extremely high exposure. Halothane, enflurane, isoflurane, desflurane, and sevoflurane may be teratogenic in rodents as a result of physiologic changes associated with the anesthesia rather than through a direct teratogenic effect.

The most consistent finding in surveys conducted to determine the reproductive success of female operating room personnel has been a questionably higher-than-expected incidence of miscarriages.

However, there are several problems in interpreting these studies. The association of obstetric problems with surgery and anesthesia in pregnant patients is also an important consideration. In the USA, at least 50,000 pregnant women each year undergo anesthesia and surgery for indications unrelated to pregnancy. The risk of abortion is clearly higher following this experience. It is not obvious, however, whether the underlying disease, surgery, anesthesia, or a combination of these factors is the cause of the increased risk

2. Carcinogenicity—Epidemiologic studies suggested an increase in the cancer rate in operating room personnel who were exposed to trace concentrations of anesthetic agents. However, no study has demonstrated the existence of a causal relationship between anesthetics and cancer. Many other factors might account for the questionably positive results seen after a careful review of epidemiologic data. Most operating rooms now use scavenging systems to remove trace concentrations of anesthetics released from anesthetic machines.

INTRAVENOUS ANESTHETICS

Intravenous nonopioid anesthetics play an important role in the practice of modern anesthesia. They are widely used to facilitate rapid induction of anesthesia and have replaced inhalation as the preferred method of anesthesia induction in most settings except for pediatric anesthesia. Intravenous agents are also commonly used to provide sedation during monitored anesthesia care and for patients in intensive care (ICU) settings. With the introduction of propofol, intravenous anesthesia also became an option for the maintenance of anesthesia. However, similar to the inhaled agents, the currently available intravenous anesthetics are not ideal anesthetic drugs in the sense of producing all and only the five desired effects (unconsciousness, amnesia, analgesia, inhibition of autonomic reflexes, and skeletal muscle relaxation). Therefore, **balanced anesthesia** with multiple drugs (inhaled anesthetics, sedative-hypnotics, opioids, neuromuscular blocking drugs) is generally used to minimize unwanted side effects.

The intravenous anesthetics used for induction of general anesthesia are lipophilic and preferentially partition into highly perfused lipophilic tissues (brain, spinal cord), which accounts for their rapid onset of action. Regardless of the extent and speed of their metabolism, termination of the effect of a single bolus is determined by redistribution of the drug into less perfused and inactive tissues such as skeletal muscle and fat. Thus, all drugs used for induction of anesthesia have a similar duration of action when administered as a single bolus dose despite significant differences in their metabolism. Figure 25–6 shows the chemical structures of common clinically used intravenous anesthetics. Table 25–2 lists pharmacokinetic properties of these and other intravenous agents.

PROPOFOL

In most countries, propofol is the most frequently administered drug for induction of anesthesia and has largely replaced barbiturates for this indication. Because its pharmacokinetic profile

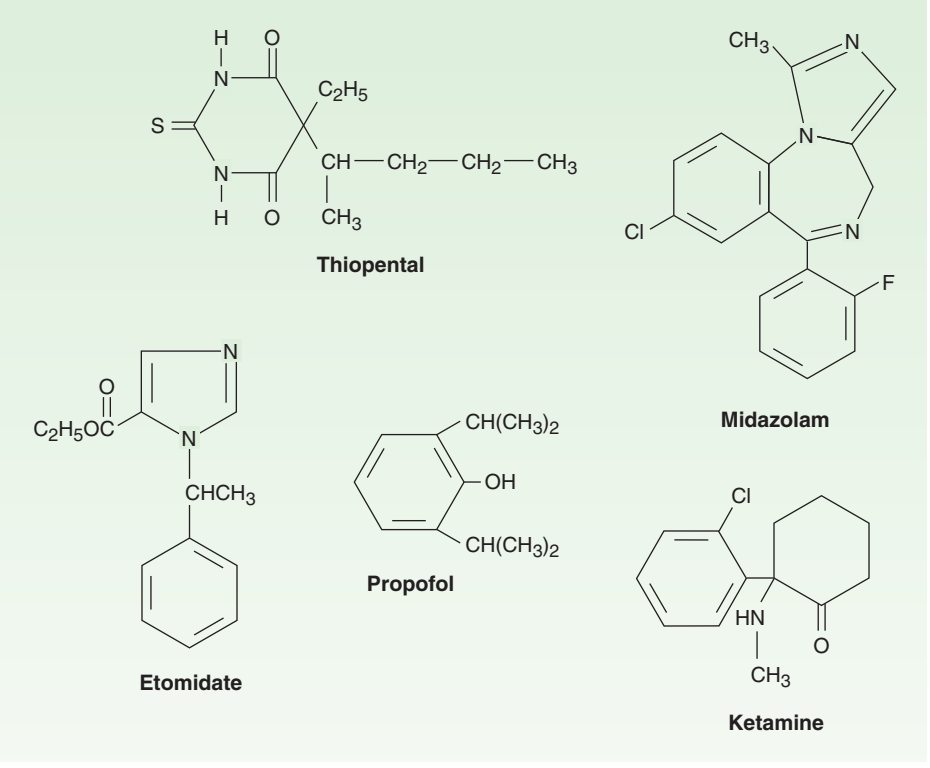

FIGURE 25–6 Chemical structures of some intravenous anesthetics.

TABLE 25–2 Pharmacokinetic properties of intravenous anesthetics.

Drug	Induction Dose (mg/kg IV)	Duration of Action (min)	V_{dss} (L/kg)	$t_{½}$ Distribution (min)	Protein Binding (%)	CL (mL/kg/min)	$t_{½}$ Elimination (h)
Dexmedetomidine	NA	NA	2–3	6	94	10–30	2–3
Diazepam	0.3–0.6	15–30	0.7–1.7	10–5	98	0.2–0.5	20–50
Etomidate	0.2–0.3	3–8	2.5–4.5	2–4	77	18–25	2.9–5.3
Ketamine	1–2	5–10	3.1	11–16	12	12–17	2–4
Lorazepam	0.03–0.1	60–120	0.8–1.3	3–10	98	0.8–1.8	11–22
Methohexital	1–1.5	4–7	2.2	5–6	73	11	4
Midazolam	0.1–0.3	15–20	1.1–1.7	7–15	94	6.4–11	1.7–2.6
Propofol	1–2.5	3–8	2–10	2–4	97	20–30	4–23
Thiopental	3–5	5–10	2.5	2–4	83	3.4	11

Note: The duration of action reflects the duration after a typical single IV dose given for induction of anesthesia. Data are for average adult patients.

CL, clearance; NA, not applicable; V_{dss}, volume of distribution at steady state.

allows for continuous infusions, propofol is also used during maintenance of anesthesia and is a common choice for sedation in the setting of monitored anesthesia care. Increasingly, propofol is also used for sedation in the ICU as well as conscious sedation and short-duration general anesthesia in locations outside the operating room (eg, interventional radiology suites, emergency department; see Box: Sedation & Monitored Anesthesia Care, earlier).

Propofol (2,6-diisopropylphenol) is an alkyl phenol with hypnotic properties that is chemically distinct from other groups of intravenous anesthetics (Figure 25–6). Because of its poor solubility in water, it is formulated as an emulsion containing 10% soybean oil, 2.25% glycerol, and 1.2% lecithin, the major component of the egg yolk phosphatide fraction. Hence, susceptible patients may experience allergic reactions. The solution appears milky white and slightly viscous, has a pH of approximately 7, and a propofol concentration of 1% (10 mg/mL). In some countries, a 2% formulation is available. Although retardants of bacterial growth are added to the formulations, solutions should be used as soon as possible (no more than 8 hours after opening the vial) and proper sterile technique is essential. The addition of metabisulfite in one of the formulations has raised concern regarding its use in patients with reactive airway disease (eg, asthma) or sulfite allergies.

The presumed mechanism of action of propofol is through potentiation of the chloride current mediated through the $GABA_A$ receptor complex.

Pharmacokinetics

Propofol is rapidly metabolized in the liver; the resulting water-soluble compounds are presumed to be inactive and are excreted through the kidneys. Plasma clearance is high and exceeds hepatic blood flow, indicating the importance of extrahepatic metabolism, which is thought to occur to a significant extent in the lungs and may account for the elimination of up to 30% of a bolus dose of the drug (Table 25–2). The recovery from propofol is more complete, with less "hangover" than that observed with thiopental, likely due to the high plasma clearance. However, as with other intravenous drugs, transfer of propofol from the plasma (central) compartment and the associated termination of drug effect after a single bolus dose are mainly the result of redistribution from highly perfused (brain) to less-well-perfused (skeletal muscle) compartments (Figure 25–7). As with other intravenous agents, awakening after an induction dose of propofol usually occurs within 8–10 minutes. The kinetics of propofol (and other intravenous anesthetics) after a single bolus dose or continuous infusion are best described by means of a three-compartment model. Such models have been used as the basis for developing systems of target-controlled infusions.

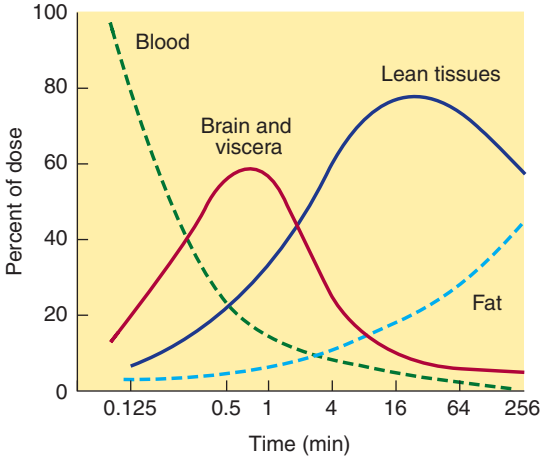

FIGURE 25–7 Redistribution of thiopental after an intravenous bolus administration. The redistribution curves for other intravenous anesthetics look similar after a bolus injection, explaining that the recovery times are similar despite remarkable differences in metabolism. Note that the time axis is not linear.

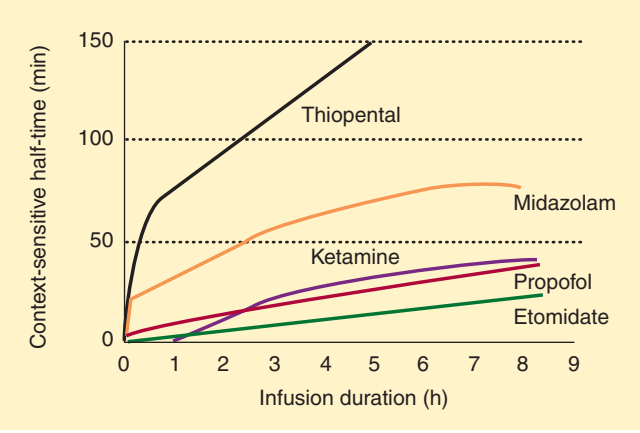

FIGURE 25–8 The context-sensitive half-time of common intravenous anesthetics. Even after a prolonged infusion, the half-time of propofol is relatively short, which makes propofol the preferred choice for intravenous anesthesia. Ketamine and etomidate have similar characteristics but their use is limited by other effects.

The **context-sensitive half-time** of a drug describes the elimination half-time after a continuous infusion as a function of the duration of the infusion and is an important factor in the suitability of a drug for use as maintenance anesthetic. The context-sensitive half-time of propofol is brief, even after a prolonged infusion, and recovery remains relatively prompt (Figure 25–8).

Organ System Effects

A. CNS Effects

Propofol acts as hypnotic but does not have analgesic properties. Although the drug leads to a general suppression of CNS activity, excitatory effects such as twitching or spontaneous movement are occasionally observed during induction of anesthesia. These effects may resemble seizure activity; however, most studies support an anticonvulsant effect of propofol, and the drug may be safely administered to patients with seizure disorders. Propofol decreases cerebral blood flow and the cerebral metabolic rate for oxygen ($CMRO_2$), which decreases intracranial pressure (ICP) and intraocular pressure; the magnitude of these changes is comparable to that of thiopental. Although propofol can produce a desired decrease in ICP, the combination of reduced cerebral blood flow and reduced mean arterial pressure due to peripheral vasodilation can critically decrease cerebral perfusion pressure.

When administered in large doses, propofol produces burst suppression in the EEG, an end point that has been used when administering intravenous anesthetics for neuroprotection during neurosurgical procedures. Evidence from animal studies suggests that propofol's neuroprotective effects during focal ischemia are similar to those of thiopental and isoflurane.

B. Cardiovascular Effects

Compared with other induction drugs, propofol produces the most pronounced decrease in systemic blood pressure; this is a result of profound vasodilation in both arterial and venous circulations leading to reductions in preload and afterload. This effect on systemic blood pressure is more pronounced with increased age, in patients with reduced intravascular fluid volume, and with rapid injection. Because the hypotensive effects are further augmented by the inhibition of the normal baroreflex response, the vasodilation only leads to a small increase in heart rate. Profound bradycardia and asystole after the administration of propofol have been described in healthy adults despite prophylactic anticholinergic drugs.

C. Respiratory Effects

Propofol is a potent respiratory depressant and generally produces apnea after an induction dose. A maintenance infusion reduces minute ventilation through reductions in tidal volume and respiratory rate, with the effect on tidal volume being more pronounced. In addition, the ventilatory response to hypoxia and hypercapnia is reduced. Propofol causes a greater reduction in upper airway reflexes than thiopental does, which makes it well suited for instrumentation of the airway, such as placement of a laryngeal mask airway.

D. Other Effects

Although propofol, unlike volatile anesthetics, does not augment neuromuscular block, studies have found good intubating conditions after propofol induction without the use of neuromuscular blocking agents. Unexpected tachycardia occurring during propofol anesthesia should prompt laboratory evaluation for possible metabolic acidosis (propofol infusion syndrome). An interesting and desirable side effect of propofol is its antiemetic activity. Pain on injection is a common complaint and can be reduced by premedication with an opioid or coadministration with lidocaine. Dilution of propofol and the use of larger veins for injection can also reduce the incidence and severity of injection pain.

Clinical Uses & Dosage

The most common use of propofol is to facilitate induction of general anesthesia by bolus injection of 1–2.5 mg/kg IV. Increasing age, reduced cardiovascular reserve, or premedication with benzodiazepines or opioids reduces the required induction dose; children require higher doses (2.5–3.5 mg/kg IV). Generally, titration of the induction dose helps to prevent severe hemodynamic changes. Propofol is often used for maintenance of anesthesia either as part of a balanced anesthesia regimen in combination with volatile anesthetics, nitrous oxide, sedative-hypnotics, and opioids or as part of a total intravenous anesthetic technique, usually in combination with opioids. Therapeutic plasma concentrations for maintenance of anesthesia normally range between 3 and 8 mcg/mL (typically requiring a continuous infusion rate between 100 and 200 mcg/kg/min) when combined with nitrous oxide or opioids.

When used for sedation of mechanically ventilated patients in the ICU or for sedation during procedures, the required plasma concentration is 1–2 mcg/mL, which can be achieved with a continuous infusion at 25–75 mcg/kg/min. Because of its pronounced respiratory depressant effect and narrow therapeutic range, propofol should be administered only by individuals trained in airway management.

Subanesthetic doses of propofol can be used to treat postoperative nausea and vomiting (10–20 mg IV as bolus or 10 mcg/kg/min as an infusion).

FOSPROPOFOL

As previously noted, injection pain during administration of propofol is often perceived as severe, and the lipid emulsion has several disadvantages. Intense research has focused on finding alternative formulations or related drugs that would address some of these problems. Fospropofol is a water-soluble prodrug of propofol, chemically described as 2,6-diisopropylphenoxymethyl phosphate disodium salt, that was licensed by the Food and Drug Administration in 2008 as a sedating agent for use in adult patients during monitored anesthesia care. The prodrug is rapidly metabolized by alkaline phosphatase, producing propofol, phosphate, and formaldehyde. The formaldehyde is metabolized by aldehyde dehydrogenase in the liver and in erythrocytes. The available fospropofol formulation is a sterile, aqueous, colorless, and clear solution that is supplied in a single-dose vial at a concentration of 35 mg/mL under the trade name Lusedra.

Pharmacokinetics & Organ System Effects

Because the active compound is propofol and fospropofol is a prodrug that requires metabolism to form propofol, the pharmacokinetics are more complex than for propofol itself. Multicompartment models with two compartments for fospropofol and three for propofol have been used to describe the kinetics.

The effect profile is similar to that of propofol, but onset and recovery are prolonged compared with propofol because the prodrug must first be converted into an active form. Although patients receiving fospropofol do not appear to experience the injection pain typical of propofol, a common adverse effect is the experience of paresthesia, often in the perianal region, which occurs in up to 74% of patients. The mechanism for this effect is unknown.

Clinical Uses & Dosage

Fospropofol is approved for sedation during monitored anesthesia care. Supplemental oxygen must be administered to all patients receiving the drug. As with propofol, airway compromise is a major concern. Hence, it is recommended that fospropofol be administered only by personnel trained in airway management. The recommended standard dosage is an initial bolus dose of 6.5 mg/kg IV followed by supplemental doses of 1.6 mg/kg IV as needed. For patients weighing more than 90 kg or less than 60 kg, 90 or 60 kg should be used to calculate the dose, respectively. The dose should be reduced by 25% in patients older than 65 years and in those with an American Society of Anesthesiologists status of 3 or 4.

BARBITURATES

This section focuses on the use of thiopental and methohexital for induction of general anesthesia; however, these barbiturate hypnotics have been largely replaced as induction agents by propofol. Other barbiturates as well as general barbiturate pharmacology are discussed in Chapter 22.

The anesthetic effect of barbiturates presumably involves a combination of enhancement of inhibitory and inhibition of excitatory neurotransmission. Although the effects on inhibitory transmission probably result from activation of the $GABA_A$ receptor complex, the effects on excitatory transmission are less well understood.

Pharmacokinetics

Thiopental and methohexital undergo hepatic metabolism, mostly by oxidation but also by *N*-dealkylation, desulfuration, and destruction of the barbituric acid ring structure. Barbiturates should not be administered to patients with acute intermittent porphyria because they increase the production of porphyrins through stimulation of aminolevulinic acid synthetase. Methohexital has a shorter elimination half-time than thiopental due to its larger plasma clearance (Table 25–2), leading to a faster and more complete recovery after bolus injection. Although thiopental is metabolized more slowly and has a long elimination half-time, recovery after a single bolus injection is comparable to that of methohexital and propofol because it depends on redistribution to inactive tissue sites rather than on metabolism (Figure 25–7). However, if administered through repeated bolus injections or continuous infusion, recovery will be markedly prolonged because elimination will depend on metabolism under these circumstances (see also context-sensitive half-time, Figure 25–8).

Organ System Effects

A. CNS Effects

Barbiturates produce dose-dependent CNS depression ranging from sedation to general anesthesia when administered as bolus injections. They do not produce analgesia; instead, some evidence suggests they may reduce the pain threshold causing hyperalgesia. Barbiturates are potent cerebral vasoconstrictors and produce predictable decreases in cerebral blood flow, cerebral blood volume, and ICP. As a result, they decrease $CMRO_2$ consumption in a dose-dependent manner up to a dose at which they suppress all EEG activity. The ability of barbiturates to decrease ICP and $CMRO_2$ makes these drugs useful in the management of patients with space-occupying intracranial lesions. They may provide neuroprotection from focal cerebral ischemia (stroke, surgical retraction, temporary clips during aneurysm surgery), but probably not from global cerebral ischemia (eg, from cardiac arrest). Except for methohexital, barbiturates decrease electrical activity on the EEG and can be used as anticonvulsants. In contrast, methohexital activates epileptic foci and may therefore be useful to facilitate electroconvulsive therapy or during the identification of epileptic foci during surgery.

B. Cardiovascular Effects

The decrease in systemic blood pressure associated with administration of barbiturates for induction of anesthesia is primarily due to peripheral vasodilation and is usually smaller than the blood pressure decrease associated with propofol. There are also direct negative inotropic effects on the heart. However, inhibition of the

baroreceptor reflex is less pronounced than with propofol; thus, compensatory increases in heart rate limit the decrease in blood pressure and make it transient. The depressant effects on systemic blood pressure are increased in patients with hypovolemia, cardiac tamponade, cardiomyopathy, coronary artery disease, or cardiac valvular disease because such patients are less able to compensate for the effects of peripheral vasodilation. Hemodynamic effects are also more pronounced with larger doses and rapid injection.

C. Respiratory Effects

Barbiturates are respiratory depressants, and a usual induction dose of thiopental or methohexital typically produces transient apnea, which will be more pronounced if other respiratory depressants are also administered. Barbiturates lead to decreased minute ventilation through reduced tidal volumes and respiratory rate and also decrease the ventilatory responses to hypercapnia and hypoxia. Resumption of spontaneous breathing after an anesthetic induction dose of a barbiturate is characterized by a slow breathing rate and decreased tidal volume. Suppression of laryngeal reflexes and cough reflexes is probably not as profound as after an equianesthetic propofol administration, which makes barbiturates an inferior choice for airway instrumentation in the absence of neuromuscular blocking drugs. Furthermore, stimulation of the upper airway or trachea (eg, by secretions, laryngeal mask airway, direct laryngoscopy, tracheal intubation) during inadequate depression of airway reflexes may result in laryngospasm or bronchospasm. This phenomenon is not unique to barbiturates but is true whenever the drug dose is inadequate to suppress the airway reflexes.

D. Other Effects

Accidental intra-arterial injection of barbiturates results in excruciating pain and intense vasoconstriction, often leading to severe tissue injury involving gangrene. Approaches to treatment include blockade of the sympathetic nervous system (eg, stellate ganglion block) in the involved extremity. If extravasation occurs, some authorities recommend local injection of the area with 0.5% lidocaine (5–10 mL) in an attempt to dilute the barbiturate concentration. Life-threatening allergic reactions to barbiturates are rare, with an estimated occurrence of 1 in 30,000 patients. However, barbiturate-induced histamine release occasionally is seen.

Clinical Uses & Dosage

The principal clinical uses of thiopental (3–5 mg/kg IV) or methohexital (1–1.5 mg/kg IV) is for induction of anesthesia (unconsciousness), which usually occurs in less than 30 seconds. Patients may experience a garlic or onion taste after administration. Barbiturates such as methohexital (20–30 mg/kg) may be administered per rectum to facilitate induction of anesthesia in mentally challenged and uncooperative pediatric patients. When a barbiturate is administered with the goal of neuroprotection, an isoelectric EEG indicating maximal reduction of $CMRO_2$ has traditionally been used as the end point. More recent data demonstrating equal protection after smaller doses have challenged this practice. The use of smaller doses is less frequently associated with hypotension, thus making it easier to maintain adequate cerebral perfusion pressure, especially in the setting of increased ICP.

BENZODIAZEPINES

Benzodiazepines commonly used in the perioperative period include midazolam, lorazepam, and less frequently, diazepam. Benzodiazepines are unique among the group of intravenous anesthetics in that their action can readily be terminated by administration of their selective antagonist, flumazenil. Their most desired effects are anxiolysis and anterograde amnesia, which are extremely useful for premedication.

The chemical structure and pharmacodynamics of the benzodiazepines are discussed in detail in Chapter 22.

Pharmacokinetics in the Anesthesia Setting

The highly lipid-soluble benzodiazepines rapidly enter the CNS, which accounts for their rapid onset of action, followed by redistribution to inactive tissue sites and subsequent termination of the drug effect. Additional information regarding the pharmacokinetics of the benzodiazepines may be found in Chapter 22.

Despite its prompt passage into the brain, midazolam is considered to have a slower effect-site equilibration time than propofol and thiopental. In this regard, intravenous doses of midazolam should be sufficiently spaced to permit the peak clinical effect to be recognized before a repeat dose is considered. Midazolam has the shortest context-sensitive half-time, which makes it the only one of the three benzodiazepine drugs suitable for continuous infusion (Figure 25–8).

Organ System Effects

A. CNS Effects

Similar to propofol and barbiturates, benzodiazepines decrease $CMRO_2$ and cerebral blood flow, but to a smaller extent. There appears to be a ceiling effect for benzodiazepine-induced decreases in $CMRO_2$ as evidenced by midazolam's inability to produce an isoelectric EEG. Patients with decreased intracranial compliance demonstrate little or no change in ICP after the administration of midazolam. Although neuroprotective properties have not been shown for benzodiazepines, these drugs are potent anticonvulsants used in the treatment of status epilepticus, alcohol withdrawal, and local anesthetic-induced seizures. The CNS effects of benzodiazepines can be promptly terminated by administration of the selective benzodiazepine antagonist flumazenil, which improves their safety profile.

B. Cardiovascular Effects

If used for the induction of anesthesia, midazolam produces a greater decrease in systemic blood pressure than comparable doses of diazepam. These changes are most likely due to peripheral vasodilation inasmuch as cardiac output is not changed. Similar to other intravenous induction agents, midazolam's effect on systemic blood pressure is exaggerated in hypovolemic patients.

C. Respiratory Effects

Benzodiazepines produce minimal depression of ventilation, although transient apnea may follow rapid intravenous administration of midazolam for induction of anesthesia, especially in the presence of opioid premedication. Benzodiazepines decrease the ventilatory response to carbon dioxide, but this effect is not usually significant if they are administered alone. More severe respiratory depression can occur when benzodiazepines are administered together with opioids. Another problem affecting ventilation is airway obstruction induced by the hypnotic effects of benzodiazepines.

D. Other Effects

Pain during intravenous and intramuscular injection and subsequent thrombophlebitis are most pronounced with diazepam and reflect the poor water solubility of this benzodiazepine, which requires an organic solvent in the formulation. Despite its better solubility (which eliminates the need for an organic solvent), midazolam may also produce pain on injection. Allergic reactions to benzodiazepines are rare to nonexistent.

Clinical Uses & Dosage

Benzodiazepines are most commonly used for preoperative medication, intravenous sedation, and suppression of seizure activity. Less frequently, midazolam and diazepam may also be used to induce general anesthesia. The slow onset and prolonged duration of action of lorazepam limit its usefulness for preoperative medication or induction of anesthesia, especially when rapid and sustained awakening at the end of surgery is desirable. Although flumazenil (8–15 mcg/kg IV) may be useful for treating patients experiencing delayed awakening, its duration of action is brief (about 20 minutes) and resedation may occur.

The amnestic, anxiolytic, and sedative effects of benzodiazepines make this class of drugs the most popular choice for preoperative medication. Midazolam (1–2 mg IV) is effective for premedication, sedation during regional anesthesia, and brief therapeutic procedures. Midazolam has a more rapid onset, with greater amnesia and less postoperative sedation, than diazepam. Midazolam is also the most commonly used oral premedication for children; 0.5 mg/kg administered orally 30 minutes before induction of anesthesia provides reliable sedation and anxiolysis in children without producing delayed awakening.

The synergistic effects between benzodiazepines and other drugs, especially opioids and propofol, can be used to achieve better sedation and analgesia but may also greatly enhance their combined respiratory depression and may lead to airway obstruction or apnea. Because benzodiazepine effects are more pronounced with increasing age, dose reduction and careful titration may be necessary in elderly patients.

General anesthesia can be induced by the administration of midazolam (0.1–0.3 mg/kg IV), but the onset of unconsciousness is slower than after the administration of thiopental, propofol, or etomidate. Delayed awakening is a potential disadvantage, limiting the usefulness of benzodiazepines for induction of general anesthesia despite their advantage of less pronounced circulatory effects.

ETOMIDATE

Etomidate (Figure 24–6) is an intravenous anesthetic with hypnotic but not analgesic effects and is often chosen for its minimal hemodynamic effects. Although its pharmacokinetics are favorable, endocrine side effects limit its use for continuous infusions. Etomidate is a carboxylated imidazole derivative that is poorly soluble in water and is therefore supplied as a 2 mg/mL solution in 35% propylene glycol. The solution has a pH of 6.9 and thus does not cause problems with precipitation as thiopental does. Etomidate appears to have GABA-like effects and seems to act primarily through potentiation of $GABA_A$-mediated chloride currents, like most other intravenous anesthetics.

Pharmacokinetics

An induction dose of etomidate produces rapid onset of anesthesia, and recovery depends on redistribution to inactive tissue sites, comparable to thiopental and propofol. Metabolism is primarily by ester hydrolysis to inactive metabolites, which are then excreted in urine (78%) and bile (22%). Less than 3% of an administered dose of etomidate is excreted as unchanged drug in urine. Clearance of etomidate is about five times that of thiopental, as reflected by a shorter elimination half-time (Table 25–2). The duration of action is linearly related to the dose, with each 0.1 mg/kg providing about 100 seconds of unconsciousness. Because of etomidate's minimal effects on hemodynamics and short context-sensitive half-time, larger doses, repeated boluses, or continuous infusions can safely be administered. Etomidate, like most other intravenous anesthetics, is highly protein bound (77%), primarily to albumin.

Organ System Effects

A. CNS Effects

Etomidate is a potent cerebral vasoconstrictor, as reflected by decreases in cerebral blood flow and ICP. These effects are similar to those produced by comparable doses of thiopental. Despite its reduction of $CMRO_2$, etomidate has failed to show neuroprotective properties in animal studies, and human studies are lacking. The frequency of excitatory spikes on the EEG after the administration of etomidate is greater than with thiopental. Similar to methohexital, etomidate may activate seizure foci, manifested as fast activity on the EEG. In addition, spontaneous movements characterized as myoclonus occur in more than 50% of patients receiving etomidate, and this myoclonic activity may be associated with seizure-like activity on the EEG.

B. Cardiovascular Effects

A characteristic and desired feature of induction of anesthesia with etomidate is cardiovascular stability after bolus injection. In this regard, decrease in systemic blood pressure is modest or absent and principally reflects a decrease in systemic vascular resistance. Therefore, the systemic blood pressure-lowering effects of etomidate are probably exaggerated in the presence of hypovolemia, and optimization of the patient's intravascular fluid volume status before induction of anesthesia should be achieved.

Etomidate produces minimal changes in heart rate and cardiac output. Its depressant effects on myocardial contractility are minimal at concentrations used for induction of anesthesia.

C. Respiratory Effects

The depressant effects of etomidate on ventilation are less pronounced than those of barbiturates, although apnea may occasionally follow rapid intravenous injection of the drug. Depression of ventilation may be exaggerated when etomidate is combined with inhaled anesthetics or opioids.

D. Endocrine Effects

Etomidate causes adrenocortical suppression by producing a dose-dependent inhibition of 11β-hydroxylase, an enzyme necessary for the conversion of cholesterol to cortisol. This suppression lasts 4–8 hours after an induction dose of the drug. Despite concerns regarding this finding, no outcome studies have demonstrated an adverse effect. However, because of its endocrine effects, etomidate is not used as continuous infusion.

Clinical Uses & Dosage

Etomidate is an alternative to propofol and barbiturates for the rapid intravenous induction of anesthesia, especially in patients with compromised myocardial contractility. After a standard induction dose (0.2–0.3 mg/kg IV), the onset of unconsciousness is comparable to that achieved by thiopental and propofol. Similar to propofol, during intravenous injection of etomidate there is a high incidence of pain, which may be followed by venous irritation. Involuntary myoclonic movements are also common but may be masked by the concomitant administration of neuromuscular blocking drugs. Awakening after a single intravenous dose of etomidate is rapid, with little evidence of any residual depressant effects. Etomidate does not produce analgesia, and postoperative nausea and vomiting may be more common than after the administration of thiopental or propofol.

KETAMINE

Ketamine (Figure 25–6) is a partially water-soluble and highly lipid-soluble phencyclidine derivative differing from most other intravenous anesthetics in that it produces significant analgesia. The characteristic state observed after an induction dose of ketamine is known as "dissociative anesthesia," wherein the patient's eyes remain open with a slow nystagmic gaze (cataleptic state). Of the two stereoisomers the *S*(+) form is more potent than the *R*(–) isomer, but only the racemic mixture of ketamine is available in the USA.

Ketamine's mechanism of action is complex, but the major effect is probably produced through inhibition of the NMDA receptor complex.

Pharmacokinetics

The high lipid solubility of ketamine ensures a rapid onset of its effect. As with other intravenous induction drugs, the effect of a single bolus injection is terminated by redistribution to inactive tissue sites. Metabolism occurs primarily in the liver and involves *N*-demethylation by the cytochrome P450 system. Norketamine, the primary active metabolite, is less potent (one third to one fifth the potency of ketamine) and is subsequently hydroxylated and conjugated into water-soluble inactive metabolites that are excreted in urine. Ketamine is the only intravenous anesthetic that has low protein binding (12%) (Table 25–2).

Organ System Effects

If ketamine is administered as the sole anesthetic, amnesia is not as complete as with the benzodiazepines. Reflexes are often preserved, but it cannot be assumed that patients are able to protect the upper airway. The eyes remain open and the pupils are moderately dilated with a nystagmic gaze. Frequently, lacrimation and salivation are increased, and premedication with an anticholinergic drug may be indicated to limit this effect.

A. CNS Effects

In contrast to other intravenous anesthetics, ketamine is considered to be a cerebral vasodilator that *increases* cerebral blood flow, as well as $CMRO_2$. For these reasons, ketamine has traditionally not been recommended for use in patients with intracranial pathology, especially increased ICP. Nevertheless, these perceived undesirable effects on cerebral blood flow may be blunted by the maintenance of normocapnia. Despite the potential to produce myoclonic activity, ketamine is considered an anticonvulsant and may be recommended for treatment of status epilepticus when more conventional drugs are ineffective.

Unpleasant emergence reactions after administration are the main factor limiting ketamine's use. Such reactions may include vivid colorful dreams, hallucinations, out-of-body experiences, and increased and distorted visual, tactile, and auditory sensitivity. These reactions can be associated with fear and confusion, but a euphoric state may also be induced, which explains the potential for abuse of the drug. Children usually have a lower incidence of and less severe emergence reactions. Combination with a benzodiazepine may be indicated to limit the unpleasant emergence reactions and also increase amnesia.

B. Cardiovascular Effects

Ketamine can produce transient but significant *increases* in systemic blood pressure, heart rate, and cardiac output, presumably by centrally mediated sympathetic stimulation. These effects, which are associated with increased cardiac workload and myocardial oxygen consumption, are not always desirable and can be blunted by coadministration of benzodiazepines, opioids, or inhaled anesthetics. Though the effect is more controversial, ketamine is considered to be a direct myocardial depressant. This property is usually masked by its stimulation of the sympathetic nervous system but may become apparent in critically ill patients with limited ability to increase their sympathetic nervous system activity.

C. Respiratory Effects

Ketamine is not thought to produce significant respiratory depression. When it is used as a single drug, the respiratory response to hypercapnia is preserved and blood gases remain stable. Transient hypoventilation and, in rare cases, a short period of apnea can follow rapid administration of a large intravenous dose for induction of anesthesia. The ability to protect the upper airway in the presence of ketamine cannot be assumed despite the presence of active airway reflexes. Especially in children, the risk for laryngospasm because of increased salivation must be considered; this risk can be reduced by premedication with an anticholinergic drug. Ketamine relaxes bronchial smooth muscles and may be helpful in patients with reactive airways and in the management of patients experiencing bronchoconstriction.

Clinical Uses & Dosage

Its unique properties, including profound analgesia, stimulation of the sympathetic nervous system, bronchodilation, and minimal respiratory depression, make ketamine an important alternative to the other intravenous anesthetics and a desirable adjunct in many cases despite the unpleasant psychotomimetic effects. Moreover, ketamine can be administered by multiple routes (intravenous, intramuscular, oral, rectal, epidural), thus making it a useful option for premedication in mentally challenged and uncooperative pediatric patients.

Induction of anesthesia can be achieved with ketamine, 1–2 mg/kg intravenously or 4–6 mg/kg intramuscularly. Though the drug is not commonly used for maintenance of anesthesia, its short context-sensitive half-time makes ketamine a candidate for this purpose. For example, general anesthesia can be achieved with the infusion of ketamine, 15–45 mcg/kg/min, plus 50–70% nitrous oxide or by ketamine alone, 30–90 mcg/kg/min.

Small bolus doses of ketamine (0.2–0.8 mg/kg IV) may be useful during regional anesthesia when additional analgesia is needed (eg, cesarean delivery under neuraxial anesthesia with an insufficient regional block). Ketamine provides effective analgesia without compromise of the airway. An infusion of a subanalgesic dose of ketamine (3–5 mcg/kg/min) during general anesthesia and in the early postoperative period may be useful to produce analgesia or reduce opioid tolerance and opioid-induced hyperalgesia. The use of ketamine has always been limited by its unpleasant psychotomimetic side effects, but its unique features make it a very valuable alternative in certain settings, mostly because of the potent analgesia with minimal respiratory depression. Most recently it has become popular as an adjunct administered at subanalgesic doses to limit or reverse opioid tolerance.

DEXMEDETOMIDINE

Dexmedetomidine is a highly selective α_2-adrenergic agonist. Recognition of the usefulness of α_2 agonists is based on observations of decreased anesthetic requirements in patients receiving chronic clonidine therapy. The effects of dexmedetomidine can be antagonized with α_2-antagonist drugs. Dexmedetomidine is the active *S*-enantiomer of medetomidine, a highly selective α_2-adrenergic agonist imidazole derivative that is used in veterinary medicine. Dexmedetomidine is water soluble and available as a parenteral formulation.

Pharmacokinetics

Dexmedetomidine undergoes rapid hepatic metabolism involving conjugation, *N*-methylation, and hydroxylation, followed by conjugation. Metabolites are excreted in the urine and bile. Clearance is high, and the elimination half-time is short (Table 25–2). However, there is a significant increase in the context-sensitive half-time from 4 minutes after a 10-minute infusion to 250 minutes after an 8-hour infusion.

Organ System Effects

A. CNS Effects

Dexmedetomidine produces its selective α_2-agonist effects through activation of CNS α_2 receptors. Hypnosis presumably results from stimulation of α_2 receptors in the locus caeruleus, and the analgesic effect originates at the level of the spinal cord. The sedative effect produced by dexmedetomidine has a different quality than that produced by other intravenous anesthetics in that it more completely resembles a physiologic sleep state through activation of endogenous sleep pathways. Dexmedetomidine is likely to be associated with a decrease in cerebral blood flow without significant changes in ICP and $CMRO_2$. It has the potential to lead to the development of tolerance and dependence.

B. Cardiovascular Effects

Dexmedetomidine infusion results in moderate decreases in heart rate and systemic vascular resistance and, consequently, a decrease in systemic blood pressure. A bolus injection may produce a transient increase in systemic blood pressure and pronounced decrease in heart rate, an effect that is probably mediated through activation of peripheral α_2 adrenoceptors. Bradycardia associated with dexmedetomidine infusion may require treatment. Heart block, severe bradycardia, and asystole have been observed and may result from unopposed vagal stimulation. The response to anticholinergic drugs is unchanged.

C. Respiratory Effects

The effects of dexmedetomidine on the respiratory system are a small to moderate decrease in tidal volume and very little change in the respiratory rate. The ventilatory response to carbon dioxide is unchanged. Although the respiratory effects are mild, upper airway obstruction as a result of sedation is possible. In addition, dexmedetomidine has a synergistic sedative effect when combined with other sedative-hypnotics.

Clinical Uses & Dosage

Dexmedetomidine is principally used for the short-term sedation of intubated and ventilated patients in an ICU setting. In the operating room, dexmedetomidine may be used as an adjunct to

general anesthesia or to provide sedation, eg, during awake fiberoptic tracheal intubation or regional anesthesia. When administered during general anesthesia, dexmedetomidine (0.5–1 mcg/kg loading dose over 10–15 minutes, followed by an infusion of 0.2–0.7 mcg/kg/h) decreases the dose requirements for inhaled and injected anesthetics. Awakening and the transition to the postoperative setting may benefit from dexmedetomidine-produced sedative and analgesic effects without respiratory depression.

OPIOID ANALGESICS

Opioids are analgesic agents and are distinct from general anesthetics and hypnotics. Even when high doses of opioid analgesics are administered, recall cannot be prevented reliably unless hypnotic agents such as benzodiazepines also are used. Opioid analgesics are routinely used to achieve postoperative analgesia and intraoperatively as part of a balanced anesthesia regimen as described earlier (see Intravenous Anesthetics). Their pharmacology and clinical use are described in greater detail in Chapter 31.

In addition to their use as part of a balanced anesthesia regimen, opioids in large doses have been used in combination with large doses of benzodiazepines to achieve a general anesthetic state, particularly in patients with limited circulatory reserve who undergo cardiac surgery. When administered in large doses, potent opioids such as fentanyl can induce chest wall (and laryngeal) rigidity, thereby acutely impairing mechanical ventilation. Furthermore, large doses of potent opioids may speed up the development of tolerance and complicate postoperative pain management.

CURRENT CLINICAL PRACTICE

The practice of clinical anesthesia requires integrating the pharmacology and the known adverse effects of these potent drugs with the pathophysiologic state of individual patients. The judgment and experience of the anesthesiologist is tested by every patient to produce the proper depth of anesthesia required to allow invasive surgery to proceed despite major medical problems present in the sickest patients.

PREPARATIONS AVAILABLE*

Desflurane (Suprane)
Liquid: 240 mL for inhalation

Dexmedetomidine (Precedex)
Parenteral: 100 mcg/mL for IV infusion

Diazepam (generic, Valium)
Oral: 2, 5, 10 mg tablets; 1 mg/mL and 5 mg/mL solution
Oral sustained-release: 15 mg capsules
Rectal: 2.5, 10, 20 mg gel
Parenteral: 5 mg/mL for injection

Droperidol (generic, Inapsine)
Parenteral: 2.5 mg/mL for IV or IM injection

Enflurane (Enflurane, Ethrane)
Liquid: 125, 250 mL for inhalation

Etomidate (Amidate)
Parenteral: 2 mg/mL for injection

Fospropofol (Lusedra)
Parenteral: 35 mg/mL in 30 mL vials

Halothane (generic, Fluothane)
Liquid: 125, 250 mL for inhalation

Isoflurane (Isoflurane, Forane)
Liquid: 100 mL for inhalation

Ketamine (generic, Ketalar)
Parenteral: 10, 50, 100 mg/mL for injection

Lorazepam (generic, Ativan)
Parenteral: 2, 4 mg/mL for injection

Methohexital (Brevital)
Parenteral: 0.5, 2.5, 5 g powder to reconstitute for injection

Midazolam (generic, Versed)
Parenteral: 1, 5 mg/mL for injection in 1, 2, 5, 10 mL vials
Oral: 2 mg/mL syrup for children

Nitrous oxide (gas, supplied in blue cylinders)

Propofol (generic, Diprivan)
Parenteral: 10 mg/mL for IV injection

Sevoflurane (generic, Ultane)
Liquid: 250 mL for inhalation

Thiopental (generic, Pentothal)
Parenteral: powder to reconstitute 20, 25 mg/mL for IV injection

*See Chapter 31 for formulations of opioid agents used in anesthesia.

REFERENCES

Eger EI II: The effect of inspired concentration on the rate of rise of alveolar concentration. Anesthesiology 1963;89:774.

Eger EI II: Uptake and distribution. In: Miller RD (editor): *Anesthesia,* 7th ed. Churchill Livingstone, 2010.

Eger EI II, Saidman LJ, Brandstater B: Minimum alveolar anesthetic concentration: A standard of anesthetic potency. Anesthesiology 1965;26:756.

Fragen RJ: *Drug Infusions in Anesthesiology.* Lippincott Williams & Wilkins, 2005.

Hemmings HC et al: Emerging molecular mechanisms of general anesthetic action. Trends Pharmacol Sci 2005;26:503.

Lugli AK, Yost CS, Kindler CH: Anesthetic mechanisms: Update on the challenge of unravelling the mystery of anaesthesia. Eur J Anaesth 2009;26:807.

Olkkola KT, Ahonen J: Midazolam and other benzodiazepines. Handb Exp Pharmacol 2008;182:335.

Reves JG et al: Intravenous anesthetics. In: Miller RD (editor): *Anesthesia,* 7th ed. Churchill Livingstone, 2010.

Rudolph U et al: Sedatives, anxiolytics, and amnestics. In: Evers AS, Maze M (editors): *Anesthetic Pharmacology: Physiologic Principles and Clinical Practice.* Churchill Livingstone, 2004.

Stoelting R, Hillier S: Barbiturates. In: Stoelting RK, Hillier SC (editors): *Pharmacology and Physiology in Anesthetic Practice.* Lippincott Williams & Wilkins, 2005.

Yasuda N et al: Kinetics of desflurane, isoflurane, and halothane in humans. Anesthesiology 1991;70:489.

CASE STUDY ANSWER

This patient has significant underlying cardiac risk involving major stressful surgery. Balanced anesthesia would begin with intravenous agents that cause minimal changes in blood pressure and heart rate such as propofol or etomidate, combined with potent analgesics such as fentanyl (see Chapter 31) to block undesirable stimulation of autonomic reflexes. Maintenance of anesthesia could incorporate inhaled anesthetics that ensure unconsciousness and amnesia, additional intravenous agents to provide intraoperative and postoperative analgesia, and, if needed, neuromuscular blocking drugs (see Chapter 27) to induce muscle relaxation. The choice of inhaled agent(s) would be made based on the desire to maintain sufficient myocardial contractility, systemic blood pressure, and cardiac output for adequate perfusion of critical organs throughout the operation. Rapid emergence from the combined effects of the chosen anesthetic drugs would facilitate the patient's return to a baseline state of heart function, breathing, and mentation.