Chapter 11 Histamine and Antihistaminics

HISTAMINE

Histamine, meaning 'tissue amine' (*histos*—tissue) is almost ubiquitously present in animal tissues and in certain plants, e.g. stinging nettle. Its pharmacology was studied in detail by Dale in the beginning of the 20th century when close parallelism was noted between its actions and the manifestations of certain allergic reactions. It was implicated as a mediator of hypersensitivity phenomena and tissue injury reactions. It is now known to play important physiological roles.

Histamine is present mostly within storage granules of *mast cells*. Tissues rich in histamine are skin, gastric and intestinal mucosa, lungs, liver and placenta. Nonmast cell histamine occurs in brain, epidermis, gastric mucosa and growing regions. Turnover of mast cell histamine is slow, while that of nonmast cell histamine is fast. Histamine is also present in blood, most body secretions, venoms and pathological fluids.

Synthesis, storage and destruction

Histamine is β imidazolylethylamine. It is synthesized locally from the amino acid histidine and degraded rapidly by oxidation and methylation (Fig. 11.1). In mast cells, histamine (positively charged) is held by an acidic protein and heparin (negatively charged) within intracellular granules. When the granules are extruded by exocytosis, Na^+ ions in e.c.f. exchange with histamine to release it free (Fig. 11.2). Increase in intracellular cAMP (caused by β adrenergic agonists and methylxanthines) inhibits histamine release. Histamine is inactive orally because liver degrades all histamine that is absorbed from the intestines.

Histamine receptors

Four types of histaminergic receptors have now been clearly delineated and cloned. Analogous to adrenergic α and β receptors, histaminergic receptors were classified

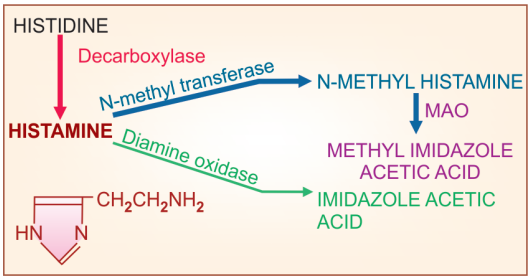


Fig. 11.1: Synthesis and degradation of histamine
MAO-Monoamine oxidase

by Asch and Schild (1966) into H_1 and H_2 : those blocked by then available antihistamines were labelled H_1. Sir James Black (1972) developed the first H_2 blocker burimamide and confirmed this classification. A third H_3 receptor, which serves primarily as an autoreceptor controlling histamine release from neurones in brain was identified in 1983. Though some selective H_3 agonists and antagonists have been produced, none has found any clinical application. Features of these 3 types of histaminergic receptor are compared in Table 11.1.

Molecular cloning has revealed yet another (H_4) receptor in 2001. It has considerable homology with H_3 receptor and binds many H_3 ligands. 4-Methyl histamine, earlier considered to be a specific H_2 agonist, has shown greater affinity and selectivity for the H_4 receptor, and is now labelled a H_4 agonist. However, the H_4 receptor is pharmacologically less distinct. Eosinophils, mast cells and basophils are the primary cells expressing H_4 receptors. Activation of H_4 receptors enhances chemotaxis of these cells. The H_4 receptor may be playing a role in allergic inflammation: H_4 antagonists are being explored as potential drugs for allergic inflammatory conditions like rhinitis and asthma. Intestines and brain are the other sites where H_4 receptors have been located.

PHARMACOLOGICAL ACTIONS

1. Blood vessels Histamine causes marked dilatation of smaller blood vessels, including arterioles, capillaries and venules. On s.c. injection

TABLE 11.1 **Distinctive features of three types of histaminergic receptors**

	H_1	H_2	H_3
1. Selective agonists (relative selectivity H_1: H_2)	2-Methyl histamine (8:1) 2-Pyridylethylamine(30:1) 2-Thiazolyl ethylamine (90: 1)	Dimaprit (1:2000) Impromidine (1:10,000)	(R) α-Methyl histamine (H_1: H_3 1:3000) Imetit
2. Selective antagonists (relative selectivity H_1: H_2)	Mepyramine (6000:1) Chlorpheniramine (15000:1)	Cimetidine (1: 500) Ranitidine (I : >500)	Thioperamide (H_1: H_3 1: 23000) Impromidine (H_2 agonist) Tiprolisant
3. Receptor type	Gq-protein coupled	Gs-protein coupled	Gi/Go-protein coupled
4. Effector pathway	PIP_2 hydrolysis → IP_3/DAG : Release of Ca^{2+} from intracellular stores; Protein kinase-C activation NO release→cGMP	Adenylyl cyclase activation — cAMP ↑—phosphorylation of specific proteins	a) Restricting Ca^{2+} influx b) K^+ channel activation c) cAMP ↓
5. Distribution in body: actions mediated	a) Smooth muscle (intestine, airway, uterus)—contraction b) Blood vessels i) Endothelium: Release of NO and, PGI_2—vasodilatation. widening of gap junctions—increased capillary permeability ii) Smooth muscle of larger vessels—vasoconstriction. c) Afferent nerve endings—stimulation d) Ganglionic cell—stimulation. e) Adrenal medulla—release of CAs. f) Brain—transmitter.	a) Gastric glands—acid secretion b) Blood vessels (smooth muscle)—dilatation c) Heart Atria: +ive chronotropy Ventricles: +ive inotropy d) Uterus (rat)—relaxation e) Brain—transmitter	a) Brain (presynaptically)—inhibition of histamine release—sedation b) Lung, spleen, skin, gastric mucosa — decrease histamine release c) Ileum—inhibition of ACh release from myenteric plexus neurones d) Certain blood vessels—inhibit NA release—vasodilatation

PIP_2—Phosphatidyl inositol bisphosphate; IP_3—Inositol trisphosphate; DAG—Diacylglycerols;

EDRF— Endothelium dependent relaxing factor; NO—Nitric oxide; PGI_2—Prostacyclin;

CAs—Catecholamines; cAMP —Cyclic 3', 5' adenosine monophosphate; ACh—Acetylcholine

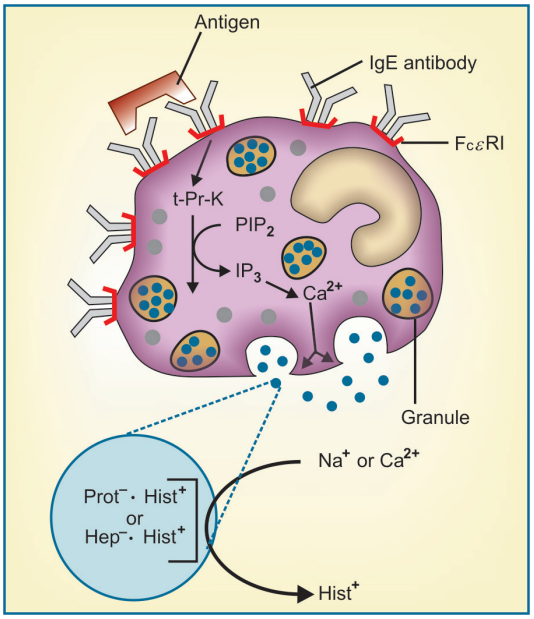


Fig. 11.2: Mechanism of antigen-antibody reaction induced release of histamine from mast cell.
In sensitized atopic individual, specific reaginic (IgE) antibody is produced and gets bound to Fc epsilon receptor I (FcεRI) on the surface of mast cells. On challenge, the antigen bridges IgE molecules resulting in transmembrane activation of a tyrosine-protein kinase (t-Pr-K) which phosphorylates and activates phospholipaseCγ. Phosphatidyl inositol bisphosphate (PIP_2) is hydrolysed and inositol trisphosphate (IP_3) is generated which triggers intracellular release of Ca^{2+}. The Ca^{2+} ions induce fusion of granule membrane with plasma membrane of the mast cell resulting in exocytotic release of granule contents. In the granule, positively charged histamine ($Hist^+$) is held complexed with negatively charged protein ($Prot^-$) and heparin (Hep^-) molecules. Cationic exchange with extracellular Na^+ (and Ca^{2+}) sets histamine free to act on the target cells.

flushing, especially in the blush area, heat, increased heart rate and cardiac output, with little or no fall in BP are produced. Rapid i.v. injection causes fall in BP which has an early short lasting H_1 and a slow but more persistent H_2 component. With low doses only the H_1 component is manifest since H_1 receptors have higher affinity. Fall in BP due to large doses is completely blocked only by a combination of H_1 and H_2 antagonists. Dilatation of cranial vessels causes pulsatile headache.

Like many other autacoids and ACh, vasodilatation caused by histamine is partly (H_1 component) indirect, mediated through 'endothelium dependent relaxing factor' (EDRF), i.e. NO; the receptor being located on the endothelial cells. H_2 receptors mediating vasodilatation are located directly on the vascular smooth muscle.

Larger arteries and veins are constricted by histamine: mediated by H_1 receptor on vascular smooth muscle. Histamine also causes increased capillary permeability due to separation of endothelial cells → exudation of plasma. This is primarily a H_1 response.

Injected intradermally, it elicits the *triple response* consisting of:

Red spot: due to intense capillary dilatation.
Wheal: due to exudation of fluid from capillaries and venules.
Flare: i.e. redness in the surrounding area due to arteriolar dilatation mediated by axon reflex.

2. Heart Direct effects of histamine on *in situ* heart are not prominent, but the isolated heart, especially of guinea pig, is stimulated—rate as well as force of contraction is increased. These are primarily H_2 responses but a H_1 mediated negative dromotropic (slowing of A-V conduction) effect has also been demonstrated.

3. Visceral smooth muscle Histamine causes bronchoconstriction; guinea pigs and patients of asthma are highly sensitive. Large doses cause abdominal cramps and colic by increasing intestinal contractions. Guineapig uterus is contracted while that or rat is relaxed; human uterus is not much affected as are most other visceral smooth muscles.

Smooth muscle contraction is a H_1 response. In few instances H_2 mediated relaxation is also seen, e.g. bronchial muscle of sheep, human bronchi after H_1 blockade.

4. Glands Histamine causes marked increase in gastric secretion—primarily of acid but also of pepsin (*see* Ch. 46). This is a direct action exerted on parietal cells through H_2 receptors and

is mediated by increased cAMP generation, which in turn activates the membrane proton pump (H^+ K^+ ATPase).

Histamine can increase other secretions also, but the effect is hardly discernable.

5. Sensory nerve endings Itching occurs when histamine is injected i.v. or intracutaneously. Higher concentrations injected more deeply cause pain. These are reflections of the capacity of histamine to stimulate nerve endings.

6. Autonomic ganglia and adrenal medulla These are stimulated and release of Adr occurs, which can cause a secondary rise in BP.

7. CNS Histamine does not penetrate blood-brain barrier—no central effects are seen on i.v. injection. However, intracerebroventricular administration produces rise in BP, cardiac stimulation, behavioural arousal, hypothermia, vomiting and ADH release. These effects are mediated through both H_1 and H_2 receptors.

PATHOPHYSIOLOGICAL ROLES

1. Gastric secretion Histamine has dominant physiological role in mediating secretion of HCl in the stomach (*see* Fig. 46.1). Nonmast cell histamine occurs in gastric mucosa, possibly in cells called 'histaminocytes' situated close to the parietal cells. This histamine has high turnover rate. It is released locally under the influence of all stimuli that evoke gastric secretion (feeding, vagal stimulation, cholinergic drugs and gastrin) and activates the proton pump (H^+K^+ ATPase) through H_2 receptors.

H_2 blockers not only suppress acid secretion induced by histamine but also markedly diminish that in response to ACh and gastrin. By a mutually synergistic interaction the three secretagogues amplify responses to each other with histamine playing the dominant role. As such, antimuscarinic drugs dampen the response to histamine and gastrin also. All three secretagogues activate the same proton pump (H^+K^+ATPase) in the parietal cell membrane, but through their own receptors.

2. Allergic phenomena Mediation of hypersensitivity reactions was the first role ascribed to histamine. It is an important, but only one of the mediators of such phenomena. Released from mast cells following AG : AB reaction on their surface (involving IgE type of reaginic antibodies; Fig. 11.2) in immediate type of hypersensitivity reactions, histamine is causative in urticaria, angioedema, bronchoconstriction and anaphylactic shock. The H_1 antagonists are effective in controlling these manifestations to a considerable extent, except asthma and to a lesser extent anaphylactic fall in BP in which leukotrienes (especially LTD_4) and PAF appear to be more important. Histamine is not involved in delayed or retarded type of allergic reactions.

3. As transmitter Histamine is believed to be the afferent transmitter which initiates the sensation of itch and pain at sensory nerve endings.

Nonmast cell histamine occurs in brain, especially hypothalamus and midbrain. It is involved in maintaining wakefulness; H_1 antihistaminics owe their sedative action to blockade of this function. In the brain H_1 agonism suppresses appetite. This may explain the appetite promoting action of certain H_1 antagonists. Histamine also appears to participate as a transmitter regulating body temperature, cardiovascular function, thirst, and possibly other functions, mainly through H_2 (postsynaptic receptors) and H_3 (presynaptic autoreceptors).

4. Inflammation Histamine is a mediator of vasodilatation and other changes that occur during inflammation. It promotes adhesion of leukocytes to vascular endothelium by expressing adhesion molecule *P-selectin* on endothelial cell surface, sequestrating leukocytes at the inflammatory site. It may also regulate microcirculation according to local needs.

5. Tissue growth and repair Because growing and regenerating tissues contain high concentrations of histamine, it has been suggested to play an essential role in the process of growth and repair.

6. Headache Histamine has been implicated in certain vascular headaches, but there is no conclusive evidence.

USES

Histamine has no therapeutic use. In the past it has been used to test acid secreting capacity of stomach, bronchial hyperreactivity in asthmatics, and for diagnosis of pheochromocytoma, but these pharmacological tests are risky and obsolete now.

Betahistine It is an orally active, somewhat H_1 selective histamine analogue, which is used to control vertigo in patients of Meniéré's disease: possibly acts by causing vasodilatation in the internal ear. It is contraindicated in asthmatics and ulcer patients.

VERTIN 8 mg tab., 1/2 to 1 tab. QID.

HISTAMINE RELEASERS

A variety of mechanical, chemical and immunological stimuli are capable of releasing histamine from mast cells.

1. Tissue damage: trauma, stings and venoms, proteolytic enzymes, phospholipase A.
2. Antigen: antibody reaction involving IgE antibodies.
3. Polymers like dextran, polyvinyl pyrrolidone (PVP).
4. Some basic drugs—tubocurarine, morphine, atropine, pentamidine, polymyxin B, vancomycin and even some antihistaminics directly release histamine without an immunological reaction.
5. Surface acting agents like Tween 80, compound 48/80 etc. The primary action of these substances is release of histamine from mast cells, therefore they are called *'histamine liberators'*. They produce an 'anaphylactoid' reaction—itching and burning sensation, flushing, urticaria, fall in BP, tachycardia, headache, colic and asthma. Most of these symptoms are controlled by a H_1 antihistaminic, better still if H_2 blocker is given together.

H_1 ANTAGONISTS (Conventional antihistaminics)

These drugs competitively antagonize actions of histamine at the H_1 receptors. Recent evidence indicates that histamine H_1 receptor exhibits some degree of constitutive activity, and the H_1 antagonists are also inverse agonists. The first compounds of this type were introduced in the late 1930s and have subsequently proliferated into an unnecessary motley of drugs. Nevertheless, they are frequently used for a variety of purposes. More commonly employed now are the less sedating/nonsedating second generation H_1 antihistamines added after 1980. Seemingly, H_1 antihistaminics have diverse chemical structures, but majority have a substituted ethylamine side chain. They are classified and listed in Table 11.2.

PHARMACOLOGICAL ACTIONS

Qualitatively all H_1 antihistaminics have similar actions, but there are quantitative differences, especially in the sedative property.

1. Antagonism of histamine They effectively block histamine induced bronchoconstriction, contraction of intestinal and other smooth muscle and triple response—especially wheal, flare and itch. Fall in BP produced by low doses of histamine is blocked, but additional H_2 antagonists are required for complete blockade of that caused by higher doses. Pretreatment with these drugs protects animals from death due to i.v. injection of large doses of histamine. Release of Adr from adrenal medulla in response to histamine is abolished. Constriction of larger blood vessel by histamine is also antagonized. Action of histamine on gastric secretion is singularly not affected by these drugs. Cyproheptadine had additional 5-HT_2 receptor blocking activity (*see* p. 174).

2. Antiallergic action Many manifestations of immediate hypersensitivity (type I reactions) are suppressed. Urticaria, itching and angioedema are well controlled. Anaphylactic fall in BP is only partially prevented. Asthma in man is practically unaffected, though anaphylactic bronchoconstriction in guinea pig is largely prevented. This tissue and species dependence of response probably reflects extent of involvement of histamine in the reaction. It is now well established that leukotrienes (C_4 and D_4) and PAF are more important mediators for human asthma.

3. CNS The older antihistamines produce variable degree of CNS depression. This appears to depend on the compound's ability to penetrate

TABLE 11.2 **Clinical classification, doses and preparations of H_1 antihistaminics**

Drug	*Dose and route*	*Preparations*
I. *HIGHLY SEDATIVE*		
Diphenhydramine	25–50 mg oral	BENADRYL 25, 50 mg cap., 12.5 mg/5ml syr.
Dimenhydrinate	25–50 mg oral,	DRAMAMINE 16 mg/5 ml syr, 50 mg tab
Promethazine	25–50 mg oral, i.m. (1 mg/kg)	PHENERGAN 10, 25 mg tab., 5 mg/ml elixer, 25 mg/ml inj
Hydroxyzine	25–50 mg oral, i.m.	ATARAX 10, 25 mg tab., 10 mg/5 ml syr, 6 mg/ml drops, 25 mg/ml inj.
II. *MODERATELY SEDATIVE*		
Pheniramine	20–50 mg oral, i.m.	AVIL 25 mg, 50 mg tab, 15 mg/5 ml syr, 22.5 mg/ml inj.
Cyproheptadine	4 mg oral	PRACTIN, CIPLACTIN 4 mg tab., 2 mg/5ml syrup,
Meclozine (Meclizine)	25–50 mg oral	In DILIGAN 12.5 mg + niacin 50 mg tab In PREGNIDOXIN 25 mg + Caffeine 20 mg tab
Cinnarizine	25–50 mg oral	STUGERON, VERTIGON 25 and 75 mg tab.
III. *MILD SEDATIVE*		
Chlorpheniramine	2–4 mg (0.1 mg/kg) oral, i.m.	PIRITON, CADISTIN 4 mg tab,
Dexchlorpheniramine	2 mg oral	POLARAMINE 2 mg tab, 0.5 mg/ 5 ml syr
Triprolidine	2.5–5 mg oral	ACTIDIL 2.5 mg tab., ACTIFED 2.5 mg with pseudoephedrine 60 mg tab.
Clemastine	1–2 mg oral	TAVEGYL 1 mg tab., 0.5 mg/5 ml syr
IV. *SECOND GENERATION ANTIHISTAMINICS*		
Fexofenadine	120–180 mg oral	ALLEGRA, ALTIVA, FEXO 120, 180 mg tab
Loratadine	10 mg oral	LORFAST, LORIDIN, LORMEG, 10 mg tab, 1 mg/ml susp.
Desloratadine	5 mg oral	DESLOR, LORDAY, NEOLORIDIN 5 mg tab
Cetirizine	10 mg oral	ALERID, CETZINE, ZIRTIN, SIZON 10 mg tab, 5 mg/5 ml syr.
Levocetirizine	5–10 mg oral	LEVOSIZ, LEVORID, TECZINE 5, 10 mg tab LEVOCET 5 mg tab, 2.5mg/5 ml syr.
Azelastine	4 mg oral 0.28 mg intranasal	AZEP NASAL SPRAY 0.14 mg per puff nasal spray
Mizolastine	10 mg oral	ELINA 10 mg tab
Ebastine	10 mg oral	EBAST 10 mg tab
Rupatadine	10 mg oral	RUPAHIST 10 mg tab

Terfenadine and astemizole are the earliest second generation H_1 antihistamines that are now banned. Cyclizine, buclizine, dimethindine, mebhydroline are conventional antihistamines that have become unavailable.

the blood-brain barrier and its affinity for the central (compared to peripheral) H_1 receptors. Individual susceptibility to different agents varies considerably. The same drug and dose may incapacitate some subjects, while others may remain alert. An overall grading of the sedative property of H_1 antihistaminics is presented in Table 11.2. Some individuals also experience stimulant effects like restlessness and insomnia. Excitement and convulsions are frequently seen at toxic doses. The second generation antihistaminics are practically nonsedating.

Certain (*see* below) H_1 antihistamines are effective in preventing motion sickness. It is not clear whether this is due to antagonism of histamine in the brain or reflects antimuscarinic property of these drugs. Promethazine also controls vomiting of pregnancy and other causes.

Promethazine and few other antihistaminics reduce tremor, rigidity and sialorrhoea of parkinsonism. Anticholinergic and sedative properties underlie the benefit.

Some older antihistamines, especially cyproheptadine, have appetite stimulating effect.

Some H_1 antihistamines are also effective antitussives (*see* Ch. 16).

4. Anticholinergic action Many H_1 blockers in addition antagonize muscarinic actions of ACh. The anticholinergic action can be graded as:

High	*Low*	*Minimal/Absent*
Promethazine	Chlorpheniramine	Fexofenadine
Diphenhydramine	Hydroxyzine	Astemizole
Dimenhydrinate	Triprolidine	Loratadine
Pheniramine	Cyproheptadine	Cetirizine
		Mizolastine

If used concurrently with atropine or its substitutes, phenothiazines, tricyclic antidepressants or disopyramide, the anticholinergic action adds up.

5. Local anaesthetic Some drugs like pheniramine, promethazine, diphenhydramine have strong while others have weak membrane stabilizing property. However, they are not used clinically as local anaesthetic because they cause irritation when injected s.c.

Membrane stabilizing activity also confers antiarrhythmic property to these compounds.

6. BP Most antihistaminics cause a fall in BP on i.v. injection (direct smooth muscle relaxation or α adrenergic blockade as in promethazine). However, this is not evident on oral administration.

PHARMACOKINETICS

The conventional H_1 antihistaminics are well absorbed from oral and parenteral routes, metabolized in the liver and excreted in urine. They are widely distributed in the body and enter brain. The newer compounds penetrate brain poorly accounting for their low/absent sedating action. Duration of action of most agents is 4–6 hours, except meclozine, chlorpheniramine, mesolastine, loratadine, cetirizine and fexofenadine which act for 12–24 hours or more.

SIDE EFFECTS AND TOXICITY

Side effects of first generation H_1 antihistaminics are frequent, but generally mild. Individuals show marked differences in susceptibility to side effects with different drugs. Some tolerance to side effects develops on repeated use.

Sedation, diminished alertness and concentration, light headedness, motor incoordination, fatigue and tendency to fall asleep are the most common. Objective testing shows impairment of psychomotor performance. Patients should be cautioned not to operate motor vehicles or machinery requiring constant attention. Alcohol synergises in producing these effects as do other CNS depressants. Few individuals become restless, nervous and are unable to sleep. Second generation compounds are largely free of CNS effects.

Regular use of conventional antihistamines is not advisable in children, because the CNS depressant property may interfere with learning and academic tasks.

Dryness of mouth, alteration of bowel movement, urinary hesitancy and blurring of vision can be ascribed to anticholinergic property.

Epigastric distress and headache may be felt. Local application can cause contact dermatitis.

Some drugs like hydroxyzine, cyclizine and fexofenadine are teratogenic in animals; but there is no evidence of excess malformations in humans. Caution is nevertheless to be exercised in prescribing an antihistaminic during pregnancy.

Acute overdose produces central excitation, tremors, hallucinations, muscular incordination, convulsions, flushing, hypotension, fever and some other features of belladonna poisoning. Death is due to respiratory and cardiovascular failure.

SECOND GENERATION ANTIHISTAMINICS

The second generation antihistaminics (SGAs) may be defined as those H_1 receptor blockers marketed after 1980 which have one or more of the following properties:

- Absence of CNS depressant property.
- Higher H_1 selectivitiy: no anticholinergic side effects.
- Additional antiallergic mechanisms apart from histamine blockade: some also inhibit late phase allergic reaction by acting on leukotrienes or by antiplatelet activating factor effect.

As per an international consensus group of experts, no compound developed so far merits labelling as 'third generation antihistaminic'.

These newer drugs have the advantage of not impairing psychomotor performance (driving etc. need not be contraindicated), produce no subjective effects, no sleepiness, do not potentiate alcohol or benzodiazepines. Some patients do complain of sedation, but incidence is similar to that with placebo. However, they have a narrow spectrum of therapeutic usefulness which is limited by the extent of involvement of histamine (acting through H_1 receptors) in the disease state. Their principal indications are:

(i) Allergic rhinitis and conjunctivitis, hay fever, pollinosis—control sneezing, runny but not blocked nose, and red, watering, itchy eyes.
(ii) Urticaria, dermographism, atopic eczema.
(iii) Acute allergic reactions to drugs and foods.

They have poor antipruritic, antiemetic and antitussive actions.

Fexofenadine It is the active metabolite of terfenadine, the first nonsedating SGA that was withdrawn because of several deaths due to polymorphic ventricular tachycarida *(Torsades de pointes)* occurring with its higher doses or when it was coadministered with CYP3A4 inhibitors (erythromycin, clarithromycin, ketoconazole, itraconazole, etc.). This toxicity is based on blockade of delayed rectifier K^+ channels in the heart at higher concentrations. Astemizole is another SGA banned for the same reason. Fexofenadine has a low propensity to block delayed rectifier K^+ channels, does not prolong QTc interval. Since it is minimally metabolized, no interaction with CYP3A4 inhibitors have been reported. It is largely free of arrhythmogenic potential, but some cases of ventricular arrhythmia in patients with preexisting long QT interval have been reported. Thus, it is not entirely safe in patients with long QT, bradycardia or hypokalemia.

Fexofenadine does not cross blood-brain barrier—does not produce sedation or impair psychomotor performance and is free of atropinic side effects. It is rapidly absorbed, excreted unchanged in urine and bile, has plasma t½ 11–16 hours and duration of action 24 hours. *Dose:* For allergic rhinitis 120 mg OD; for urticaria and other skin allergies 180 mg OD.

Loratadine Another long-acting selective peripheral H_1 antagonist which lacks CNS depressant effects and is fast acting. It is partly metabolized by CYP3A4 to an active metabolite with a longer t½ of 17 hr, but has not produced cardiac arrhythmia in overdose, though seizures are reported. No interaction with macrolides or antifungals has been noted. Good efficacy has been reported in urticaria and atopic dermatitis.

Desloratadine It is the major active metabolite of loratadine effective at half the dose. Non-interference with psychomotor performance and cardiac safety are documented.

Cetirizine It is a metabolite of hydroxyzine with marked affinity for peripheral H_1 receptors; penetrates brain poorly, but mild sedation and subjective somnolence is experienced by many recipients. It is not metabolized; does not prolong

cardiac action potential or produce arrhythmias when given with erythromycin/ketoconazole.

Cetirizine in addition inhibits release of histamine and of cytotoxic mediators from platelets as well as eosinophil chemotaxis during the secondary phase of the allergic response. Thus, it may benefit allergic disorders by other actions as well. It attains high and longer lasting concentration in skin, which may be responsible for superior efficacy in urticaria/atopic dermatitis, as well as for once daily dosing despite elimination t½ of 7–10 hr. It is indicated in upper respiratory allergies, pollinosis, urticaria and atopic dermatitis; also used as adjuvant in seasonal asthma.

Levocetirizine is the active R(–) enantiomer of cetirizine. It is effective at half the dose and appears to produce less sedation and other side effects.

Azelastine This newer H_1 blocker has good topical activity; in addition it inhibits histamine release and inflammatory reaction triggered by LTs and PAF. After intranasal application it has been shown to down regulate intracellular adhesion molecule-1 (ICAM-1) expression on nasal mucosa. Its t½ is 24 hr, but action lasts longer due to active metabolite. Its metabolism is inhibited by CYP 3A4 inhibitors. Given by nasal spray for seasonal and perennial allergic rhinitis it provides quick symptomatic relief lasting 12 hr. Stinging in the nose and altered taste perception are the local side effects. Some somnolence has been reported on nasal application and a tendency to weight gain noted after oral use.

Mizolastine This nonsedating antihistaminic is effective in allergic rhinitis and urticaria by single daily dosing despite a t½ of 8–10 hr and no active metabolite.

Ebastine Another newer SGA that rapidly gets converted to the active metabolite carbastine having a t½ of 10–16 hr. It is nonsedating and active in nasal and skin allergies. Animal studies have found it to prolong Q-Tc interval which makes it liable to arrhythmogenic potential and CYP3A4 interaction, but actual reports are still few.

Rupatadine This recently introduced antihistaminic has additional PAF antagonistic property, and is indicated in allergic rhinitis.

USES

The uses of H_1 antihistaminics are based on their ability to block certain effects of histamine released endogeneously, as well as on sedative and anticholinergic properties.

1. *Allergic disorders* Antihistaminics do not suppress AG: AB reaction, but block the effects of released histamine—are only palliative. They effectively control certain immediate type of allergies, e.g. itching, urticaria, seasonal hay fever, allergic conjunctivitis and angioedema of lips, eyelids, etc. However, their action is slow—Adr alone is life-saving in laryngeal angioedema, though intravenously administered antihistaminic may have adjuvant value. Similarly, they cannot be relied upon in anaphylactic shock and have a secondary place to Adr. Benefits are less marked in perennial vasomotor rhinitis, atopic dermatitis and chronic urticarias; combination with an H_2 antagonist succeeds in some cases of chronic urticaria not responding to H_1 antagonist alone. The antihistaminics are ineffective in bronchial asthma: reasons may be—

(i) Leukotrienes (C_4, D_4) and PAF are more important mediators than histamine.
(ii) Concentration of antihistamines attained at the site may not be sufficient to block high concentration of histamine released locally in the bronchi.

Certain newer compounds like cetirizine have adjuvant role in seasonal asthma.

Antihistaminics are also ineffective in other types of humoral and cell mediated allergies because histamine is not involved. They do suppress urticaria and swellings in serum sickness, but have no effect on other components of the syndrome.

Type I hypersensitivity reactions to drugs (except asthma and anaphylaxis) are suppressed. Some skin rashes also respond.

2. *Other conditions involving histamine* Antihistaminics block symptoms produced by histamine liberators; afford symptomatic relief in insect bite and ivy poisoning. Abnormal dermographism is suppressed. They have prophylactic value in blood/saline infusion induced rigor.

3. *Pruritides* Many conventional antihistamines have antipruritic action independent of H_1 antagonism. Though relief is often incomplete, older antihistaminics chlorpheniramine, diphenhydramine, cyproheptadine remain the first choice drugs for idiopathic pruritus.

4. *Common cold* Antihistaminics do not affect the course of the illness but may afford symptomatic relief by anticholinergic (reduce rhinorrhoea) and sedative actions. The newer nonsedating antihistamines are less effective in this respect.

5. *Motion sickness* Promethazine, diphenhydramine, dimenhydrinate and meclozine have prophylactic value in milder types of motion sickness; should be taken one hour before starting journey. Promethazine can also be used in morning sickness, drug induced and postoperative vomiting, radiation sickness.

An 'off label' (unapproved) use of cyproheptadine is often made in anorectic/convalescent patients for improving appetite. Such use in underweight children is inappropriate, because its CNS depressant action can affect learning.

6. *Vertigo* Cinnarizine is the H_1 antihistamine having additional anticholinergic, anti-5-HT, sedative and vasodilator properties which has been widely used in vertigo. It modulates Ca^{2+} fluxes and attenuates vasoconstrictor action of many endogenous mediators.

Cinnarizine inhibits vestibular sensory nuclei in the inner ear, suppresses postrotatory labyrinthine reflexes, possibly by reducing stimulated influx of Ca^{2+} from endolymph into the vestibular sensory cells. Beneficial effects have been reported in Méniére's disease and other types of vertigo. Side effects are sedation and mild g.i. upset.

Dimenhydrinate is another effective antivertigo antihistaminic.

DRUGS FOR VERTIGO

The therapy of vertigo occurring in Méniére's disease and other conditions is imperfect. A variety of approaches have been tried and have met with only partial success.

1. Labyrinthine suppressants They suppress end-organ receptors or inhibit central cholinergic pathway (in vestibular nuclei).

(a) *Antihistaminics* (with anticholinergic action)—cinnarizine, dimenhydrinate, diphenhydramine, promethazine.
(b) *Anticholinergics*—atropine, hyoscine.
(c) *Antiemetic phenothiazines*—prochlorperazine, thiethylperazine.

2. Vasodilators They improve blood flow to labyrinth and brainstem—betahistine, codergocrine, nicotinic acid.

3. Diuretics They decrease labyrinthine fluid pressure—acetazolamide, thiazides, furosemide.

4. Anxiolytics, antidepressants These drugs appear to modify the sensation of vertigo—diazepam, amitriptyline.

5. Corticosteroids They suppress intralabyrinthine edema due to viral infection or other causes.

Parenteral prochlorperazine is the most effective drug for controlling violent vertigo and vomiting.

7. *Preanaesthetic medication* Promethazine has been used for its anticholinergic and sedative properties.

8. *Cough* Antihistaminics like chlorpheniramine, diphenhydramine and promethazine are constituents of many popular cough remedies. They have no selective cough suppressant action, but may afford symptomatic relief by sedative and anticholinergic property (*see* Ch. 16).

9. *Parkinsonism* Promethazine and some others afford mild symptomatic relief in early cases—based on anticholinergic and sedative property.

10. *Acute muscle dystonia* Caused by antidopaminergic-antipsychotic drugs is promptly relieved by parenteral promethazine, diphenhydramine or hydroxyzine. This is again based on central anticholinergic action of the drugs.

11. *As sedative, hypnotic, anxiolytic* Antihistamines with CNS depressant action have been used as sedative and to induce sleep, especially in children. However, promethazine has produced serious respiratory depression in young children; few deaths are on record; it is not indicated in children aged 2 years or less. For promoting sleep, antihistaminics are not as dependable as

benzodiazepines. Hydroxyzine has been used in anxiety associated with autonomic manifestations.

(Combinations of antihistaminics with antidiarrhoeals or bronchodilators, or those containing more than one antihistaminic are banned in India.)

H_2 antagonist The first H_2 blocker *Burimamide* was developed by Black in 1972. *Metiamide* was the next, but both were not found suitable for clinical use. *Cimetidine* was introduced in 1977 and gained wide usage. *Ranitidine, famotidine, roxatidine,* and many others have been added subsequently. They are primarily used in peptic ulcer, gastroesophageal reflux and other gastric hypersecretory states. They are described in Ch. 46.

H_3 antagonist Though some selective H_3 antagonists have been produced, they have not found any clinical utility.

☞ PROBLEM DIRECTED STUDY

11.1 A taxi driver aged 30 years presented with sudden onset running and itchy nose, bouts of sneezing, partial nasal blockage, redness and watering from the eyes, but no fever, bodyache or malaise. He gave history of similar episodes occurring off and on during the spring season. A diagnosis of seasonal allergic rhinitis was made and the doctor decided to prescribe antiallergic medication.

(a) Which antiallergic medicine would be suitable for this patient? Which antiallergic drugs should be avoided?

(see Appendix-1 for solution)

Chapter 12 5-Hydroxytryptamine, its Antagonists and Drug Therapy of Migraine

5-HYDROXYTRYPTAMINE (5-HT, Serotonin)

Serotonin was the name given to the vasoconstrictor substance which appeared in the serum when blood clotted and *Enteramine* to the smooth muscle contracting substance present in enterochromaffin cells of gut mucosa. In the early 1950s both were shown to be *5-hydroxytryptamine* (5-HT). About 90% of body's content of 5-HT is localized in the intestines; most of the rest is in platelets and brain. It is also found in wasp and scorpion sting, and is widely distributed in invertebrates and plants (banana, pear, pineapple, tomato, stinging nettle, cowhage).

SYNTHESIS, STORAGE AND DESTRUCTION

5-HT is β-aminoethyl-5-hydroxyindole. It is synthesized from the amino acid tryptophan and degraded primarily by MAO and to a small extent by a dehydrogenase (Fig. 12.1).

There is close parallelism between CAs and 5-HT. The decarboxylase is non-specific, acts on DOPA as well as 5-hydroxytryptophan (5-HTP)

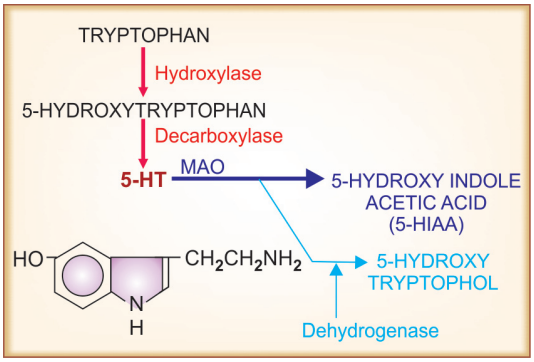


Fig. 12.1: Synthesis and degradation of 5-hydroxytryptamine (5-HT)

to produce DA and 5-HT respectively. Like NA, 5-HT is actively taken up by an amine pump *serotonin transporter (SERT),* a Na^+ dependent carrier, which operates at the membrane of platelets (therefore, 5-HT does not circulate in free form in plasma) and serotonergic nerve endings. This pump is inhibited by selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs). Platelets do not synthesize 5-HT but acquire it by uptake during passage through intestinal blood vessels. Again like CAs, 5-HT is stored within storage vesicles, and its uptake at the vesicular membrane by *vesicular monoamine transporter (VMAT-2)* is inhibited by reserpine, which causes depletion of CAs as well as 5-HT. The degrading enzyme MAO is also common for both. The isoenzyme MAO-A preferentially metabolizes 5-HT.

SEROTONERGIC (5-HT) RECEPTORS

Gaddum and Picarelli (1957) classified 5-HT receptors into musculotropic (D type) and neurotropic (M type) on the basis of thier blockade by *D*ibenzyline (phenoxybenzamine) and *M*orphine. The classical 5-HT antagonists methysergide and cyproheptadine blocked D type receptors. Subsequently 5-HT receptors were differentiated by their high or low affinity for [^{3}H] 5-HT in radioligand binding studies. The present system of classifying 5-HT receptors is based on molecular characterization and cloning of the receptor cDNAs. Some subtypes of 5-HT receptors have specific tissue distribution, but certain tissues express more than one subtype.

Four families of 5-HT receptors (5-HT_1, 5-HT_2, 5-HT_3, 5-HT_{4-7}) comprising of 14 receptor subtypes have so far been recognized. However, only some of these have been functionally correlated. Selective agonists/antagonists have

been defined only for these subtypes. Knowledge of subtypes of 5-HT receptors has assumed importance because some newly developed therapeutically useful drugs can only be described in terms of 5-HT receptor subtype selective agonists or antagonists.

All 5-HT receptors (except 5-HT_3) are G protein coupled receptors which function through decreasing (5-HT_1) or increasing (5-HT_4, 5-HT_6, 5-HT_7) cAMP production or by generating IP_3/DAG (5-HT_2) as second messengers. The 5-HT_3 is a ligand gated cation (Na^+,K^+) channel which on activation elicits fast depolarization.

5-HT_1 Receptors Five subtypes (5-$HT_{1A, B, D, E, F}$) have been identified. The 5-HT_{1C} receptor is now designated 5HT_{2c}. All subtypes of 5-HT_1 receptor couple with Gi/Go protein and inhibit adenylyl cyclase; 5-HT_{1A} in addition activates K^+ channels (resulting in hyperpolarization) and inhibits Ca^{2+} channels. These receptors function primarily as autoreceptors in brain—inhibit firing of 5-HT neurones or release of 5-HT from nerve endings.

The most important location of 5-HT_{1A} receptor is somatodendritic synapses in raphe nuclei of brain stem; their activation serves to reduce firing of raphe neurones. Hippocampus is another important site. The antianxiety drug *buspirone* acts as a partial agonist of 5-HT_{1A} receptor. The 5-HT_{1D} receptor has been shown to regulate dopaminergic tone in substantia nigra–basal ganglia, and 5-$HT_{1D/1B}$ (the same receptor is 5-HT_{1D} in humans and 5-HT_{1B} in rat) to cause constriction of cranial blood vessels. The antimigraine drug *sumatriptan* is a selective 5-$HT_{1D/1B}$ agonist. Other functions subserved by 5-HT_{1D} receptors are inhibition of 5-HT release from forebrain serotonergic neurones, NA release from sympathetic nerve endings and that of inflammatory neuropeptides from nerve endings in cranial blood vessels.

5-HT_2 Receptors There are 3 subtypes of 5-HT_2 receptor; all are coupled to Gq protein→activate phospholipase C and function through generation of IP_3/DAG. 5-HT_{2A} receptor also inhibits K^+ channels resulting is slow depolarization of neurones. α-methyl 5-HT is a selective agonist for all 3 subtypes.

5-HT_{2A} is the most widely expressed postjunctional 5-HT receptor (designated earlier as D type) located on vascular and visceral smooth muscle, platelets and cerebral neurones especially prefrontal cortex. It mediates most of the direct actions of 5-HT like vasoconstriction, intestinal, uterine and bronchial contraction, platelet aggregation and activation of cerebral neurones. *Ketanserin* is a 5-HT_2 antagonist more selective for 5-HT_{2A}.

Contraction of rat gastric fundus is mediated by 5-HT_{2B} receptor.

5-HT_{2C} receptor is located on vascular endothelium—elicits vasodilatation through EDRF release. Choroid plexus expresses large number of 5-HT_{2C} receptors which may regulate CSF formation..

5-HT_3 Receptor This is the neuronal 5-HT receptor which rapidly depolarizes nerve endings by opening the cation channel located within it and corresponds to the original M type receptor. It mediates the indirect and reflex effects of 5-HT at:

(i) Somatic and autonomic nerve endings → pain, itch, coronary chemoreflex (bradycardia, fall in BP due to withdrawal of sympathetic tone, respiratory stimulation or apnoea elicited by stimulation of receptors in the coronary bed), other visceral reflexes.

(ii) Nerve endings in myenteric plexus → augmentation of peristalsis, emetic reflex.

(iii) Area postrema and nucleus tractus solitarious in brainstem → nausea, vomiting.

Ondansetron is a selective 5-HT_3 antagonist which inhibits vomiting by blocking these receptors in the brainstem as well as in gut wall. 2-Methyl 5-HT is a selective 5-HT_3 agonist.

5-$HT_{4–7}$ Receptors The 5-HT_4 receptor couples to Gs protein, activates adenylyl cyclase and has been demonstrated in the mucosa, plexuses and smooth muscle of the gut → probably involved in augmenting intestinal secretion and peristalsis. It is also located in brain, especially hippocampus and the colliculi where it causes slow depolarization by decreasing K^+ conductance.

Cisapride and *renzapride* are selective 5-HT_4 agonists.

The recently cloned 5-HT_5, 5-HT_6 and 5-HT_7 receptors are closely related to the 5-HT_4 receptor. These are mainly located in specific brain areas, but their functional role is not known. An interesting finding is that *clozapine* (atypical antipsychotic) has high affinity for 5-HT_6 and 5-HT_7 receptors in addition to being a 5-$HT_{2A/2C}$ antagonist.

ACTIONS

5-HT is a potent depolarizer of nerve endings. It thus exerts direct as well as reflex and indirect effects. Tachyphylaxis is common with repeated doses of 5-HT. The overall effects therefore are often variable.

1. CVS Arteries are constricted (by direct action on vascular smooth muscle) as well as dilated (through EDRF release) by 5-HT, depending on the vascular bed and the basal tone. In addition, 5-HT releases Adr from adrenal medulla, affects ganglionic transmission and evokes cardiovascular reflexes. The net effect is complex. Larger arteries and veins are characteristically constricted. In the microcirculation 5-HT dilates arterioles and constricts venules:

Salient features of important 5-HT receptor subtypes

5-HT$_1$:	Autoreceptors; inhibit serotonergic neural activity in brain. *5-HT$_{1A}$*—present in raphe nuclei and hippocampus; buspirone (antianxiety) may act through these receptors. *5-HT$_{1D/1B}$*—Constricts cranial blood vessels and inhibits release of inflammatory neuropeptides in them; sumatriptan (antimigraine) acts through these receptors.
5-HT$_{2A}$:	Previously D type receptor; most important postjunctional receptor mediating direct actions of 5-HT like vascular and visceral smooth muscle contraction, platelet aggregation, neuronal activation in brain; ketanserin blocks these receptors.
5-HT$_3$:	Previously M type receptor; depolarizes neurones by gating cation channels; elicits reflex effects of 5-HT—emesis, gut peristalsis, bradycardia, transient hypotension, apnoea, pain, itch; ondansetron (antiemetic) acts by blocking these receptors.
5-HT$_4$:	Mediate intestinal secretion, augmentation of peristalsis. Renzapride (prokinetic) is a selective 5-HT$_4$ agonist.

capillary pressure rises and fluid escapes. The direct action to increase capillary permeability is feeble.

Isolated heart is stimulated by 5-HT: both directly and by release of NA from nerve endings. In intact animals, bradycardia is mostly seen due to activation of coronary chemoreflex (Bezold Jarisch reflex) through action on vagal afferent nerve endings in the coronary bed, evoking bradycardia, hypotension and apnoea.

BP: a triphasic response is classically seen on i.v. injection of 5-HT in animals.

- Early sharp fall in BP—due to coronary chemoreflex.
- Brief rise in BP—due to vasoconstriction and increased cardiac output.
- Prolonged fall in BP—due to arteriolar dilatation and extravasation of fluid.

However, 5-HT is not involved in the physiological regulation of BP.

2. Visceral smooth muscles 5-HT is a potent stimulator of g.i.t., both by direct action as well as through enteric plexuses. Several subtypes of 5-HT recep-tors are present in the gut (*See* box). Peristalsis is increased and diarrhoea can occur (also due to increased secretion).

It constricts bronchi, but is less potent than histamine. Action on other smooth muscles in man are feeble and inconsistent.

3. Glands 5-HT inhibits gastric secretion (both acid and pepsin), but increases mucus production. It thus has ulcer protective property. Effect on other glandular secretions is not significant.

5-HT receptor function in the gut

5-HT$_{2A}$	: intestinal smooth muscle—contraction.
5-HT$_3$	: fast depolarization of enteric plexus neurones; release of 5-HT from entero-chromaffin cells.
5-HT$_4$	: lower esophageal sphincter—contraction; enteric plexus—ACh release—enhanced peristalsis; intestinal mucosa—secretion.
5-HT$_1$	: slow depolarization of enteric plexus neurones.

4. Nerve endings and adrenal medulla Afferent nerve endings are activated causing tingling and pricking sensation, as well as pain. Depolarization of visceral afferents elicits respiratory and cardiovascular reflexes, nausea and vomiting. 5-HT is less potent than histamine in releasing CAs from adrenal medulla.

5. Respiration A brief stimulation of respiration (mostly reflex from bronchial afferents) and hyperventilation are the usual response, but large doses can cause transient apnoea through coronary chemoreflex.

6. Platelets By acting on 5-HT$_{2A}$ receptors 5-HT causes changes in shape of platelets, but is a weak aggregator. However, it does not induce the release reaction.

7. CNS Injected i.v., 5-HT does not produce central effects because of poor entry across blood-brain barrier. However, it serves as a transmitter, primarily inhibitory. Direct injection in the brain produces sleepiness, changes in body temperature, hunger and a variety of behavioural effects.

PATHOPHYSIOLOGICAL ROLES

1. *Neurotransmitter* 5-HT is a confirmed neurotransmitter in the brain; brain 5-HT has a fast turnover rate. Cells containing 5-HT are present in the raphe nuclei of brainstem, substantia nigra and few other sites—send axons rostrally (to limbic system, cortex and neostriatum) as well as caudally to spinal cord. 5-HT appears to be involved in sleep, temperature regulation, thought, cognitive function, behaviour and mood, appetite, vomiting and pain perception. Some serotonergic neurones are present in intestines also.

Experimental evidence from pharmacological manipulation of 5-HT metabolism, genetic models (like knock out mice), as well as therapeutic effect of selective serotonin reuptake inhibitors (SSRIs) and TCAs etc. strongly suggest a role of 5-HT in the pathogenesis of anxiety, depression, aggression and other behavioral disorders in humans.

2. *Precursor of melatonin* 5-HT is the precursor of melatonin in pineal gland. It is believed to regulate the biological clock and maintain circadian rhythm.

3. *Neuroendocrine function* The hypothalamic neurones that control release of anterior pituitary hormones are probably regulated by serotonergic mechanism.

4. *Nausea and vomiting* Especially that evoked by cytotoxic drugs or radiotherapy is mediated by release of 5-HT and its action on 5-HT_3 receptors in the gut, area postrema and nucleus tractus solitarious.

5. *Migraine* 5-HT is said to initiate the vasoconstrictor phase of migraine and to participate in neurogenic inflammation of the affected blood vessels. Methysergide (5-HT antagonist) is an effective prophylactic and sumatriptan ($5\text{-HT}_{1B/1D}$ agonist) can control an attack. However, the role of 5-HT in this condition is not precisely known.

6. *Haemostasis* Platelets release 5-HT during aggregation at the site of injury to blood vessel. Acting in concert with collagen and other mediators, this 5-HT accelerates platelet aggregation and clot formation. Thus, it serves to amplify the response. Its contractile action appears to promote retraction of the injured vessel. Both the above actions contribute to haemostasis.

7. *Raynaud's phenomenon* Release of 5-HT from platelets may trigger acute vasospastic episodes of larger arteries involved in Raynaud's phenomena. Ketanserin has prophylactic value.

8. *Variant angina* Along with thromboxane A_2, 5-HT released from platelets has been implicated in causing coronary spasm and variant angina. However, the inefficacy of anti 5-HT drugs in this condition points to the involvement of other mediators.

9. *Hypertension* Increased responsiveness to 5-HT as well as its reduced uptake and clearance by platelets has been demonstrated in hypertensive patients. Ketanserin has antihypertensive property. 5-HT has been held responsible for preeclamptic rise in BP.

10. *Intestinal motility* Enterochromaffin cells and 5-HT containing neurones may regulate peristalsis and local reflexes in the gut. This system appears to be activated by intestinal distension and vagal efferent activity.

11. *Carcinoid syndrome* The carcinoid tumours produce massive quantities of 5-HT. Bowel hypermotility and bronchoconstriction in carcinoid is due to 5-HT but flushing and hypotension are probably due to other mediators. Pellagra may occur due to diversion of tryptophan for synthesizing 5-HT.

Use Due to widespread and variable actions, 5-HT has no therapeutic use.

DRUGS AFFECTING 5-HT SYSTEM

1. *5-HT precursor* Tryptophan increases brain 5-HT and produces behavioural effects because tryptophan hydroxylase in brain is not saturated by the amount of tryptophan available physiologically.

2. *Synthesis inhibitor* p-Chlorophenylalanine (PCPA) selectively inhibits tryptophan hydroxylase (rate limiting step) and reduces 5-HT level in tissues. It is not used clinically due to high toxicity.

3. *Uptake inhibitor* Tricyclic antidepressants inhibit 5-HT uptake along with that of NA. The selective serotonin reuptake inhibitors (SSRI) like fluoxetine, sertraline, etc. inhibit only 5-HT reuptake and have antidepressant-antianxiety property.

4. *Storage inhibitor* Reserpine blocks 5-HT (as well as NA) uptake into storage vesicles by inhibiting VMAT-2, and causes depletion of all monoamines. Fenfluramine selectively releases 5-HT by promoting its reverse transport at serotonergic nerve endings in the brain, followed by its prolonged depletion, and has anorectic property.

5. *Degradation inhibitor* Nonselective MAO inhibitor (tranylcypromine) and selective MAO-A inhibitor (chlorgyline) increase 5-HT content by preventing its degradation.

6. *Neuronal degeneration* 5, 6 dihydroxytryptamine selectively destroys 5-HT neurones.

7. *5-HT receptor agonists* A diverse range of compounds producing a variety of actions have been found to activate one or more subtypes of 5-HT receptors. Notable among these are:

(i) *D-Lysergic acid diethyl amide (LSD)*—Synthesized as an ergot derivative LSD was found to be an extremely potent hallucinogen. It is a nonselective 5-HT agonist—activates many subtypes of 5-HT receptors including 5-HT_{1A} on raphe cell bodies, 5-$HT_{2A/2C}$ (probably responsible for the hallucinogenic effect) and 5-HT_{5-7} in specific brain areas. However, it antagonizes 5-HT_{2A} receptors in the ileum. A number of other hallucinogens also interact with brain 5-HT receptors.

(ii) *Azapirones* like buspirone, gepirone and ipsapirone are a novel class of antianxiety drugs which do not produce sedation. They act as partial agonists of 5-HT_{1A} receptors in the brain.

(iii) *Sumatriptan* and other triptans are selective 5-$HT_{1D/1B}$ agonists, constrict cerebral blood vessels and have emerged as the most effective treatment of acute migraine attacks.

(iv) *Cisapride* This prokinetic drug which increases gastrointestinal motility is a selective 5-HT_4 agonist. Renzapride is still more selective for 5-HT_4 receptors.

8. *5-HT receptor antagonists* A variety of drugs block serotonergic receptors; many are nonselective, but some newer ones are highly subtype selective.

5-HT ANTAGONISTS

The ability to antagonize at least some actions of 5-HT is found in many classes of drugs, e.g. ergot derivatives (ergotamine, LSD, 2-bromo LSD, methysergide), adrenergic α blockers (phenoxybenzamine), antihistaminics (cyproheptadine, cinnarizine), chlorpromazine, morphine, etc., but these are nonselective and interact with several other receptors as well. Many are partial agonists or antagonize certain actions of 5-HT but mimic others. The salient features of drugs which have been used clinically as 5-HT antagonists and some newly developed selective antagonists are described below:

1. Cyproheptadine It primarily blocks 5-HT_{2A} receptors and has additional H_1 antihistaminic, anticholinergic and sedative properties (*see* Ch. 11). Like other antihistaminics, it has been used in allergies and is a good antipruritic, but the anti 5-HT action has no role in these conditions. It increases appetite and has been used in children and poor eaters to promote weight gain. The H_1 antihistaminic action and an action on growth hormone secretion has been suggested to account for this.

The anti 5-HT activity of cyproheptadine has been utilized in controlling intestinal manifestations of carcinoid and postgastrectomy dumping syndromes as well as in antagonizing priapism/orgasmic delay caused by 5-HT uptake inhibitors like fluoxetine and trazodone.

Side effects drowsiness, dry mouth, confusion, ataxia, weight gain.

2. Methysergide It is chemically related to ergot alkaloids; antagonizes action of 5-HT on smooth muscles including that of blood vessels, without producing other ergot like effects: does not interact with α adrenergic or dopamine receptors. Methysergide is a potent 5-$HT_{2A/2C}$ antagonist with some tissue specific agonistic actions as well; but is nonselective—acts on 5-HT_1 receptors also. It has been used for migraine prophylaxis, carcinoid and postgastrectomy dumping syndrome. Prolonged use has caused abdominal, pulmonary and endocardial fibrosis, because of which it has gone into disrepute.

3. Ketanserin It has selective 5-HT_2 receptor blocking property with negligible action on 5-HT_1, 5-HT_3 and 5 HT_4

receptors and no partial agonistic activity. Among 5-HT_2 receptors, blockade of 5-HT_{2A} is stronger than 5-HT_{2C} blockade. 5-HT induced vasoconstriction, platelet aggregation and contraction of airway smooth muscle are antagonized. It has additional weak α_1, H_1 and dopaminergic blocking activities.

Ketanserin is an effective antihypertensive, but α_1 adrenergic blockade appears to be causative rather than 5-HT_{2A} blockade.

Trials of Ketanserin in vasospastic conditions have shown symptomatic improvement only in Raynaud's disease.

Ritanserin is a relatively more 5-HT_{2A} selective congener of ketanserin.

4. Clozapine In addition to being a dopaminergic antagonist (weaker than the typical neuroleptics), this atypical antipsychotic is a 5-$HT_{2A/2C}$ blocker (*see* Ch. 32). Clozapine may also exert inverse agonist activity at cerebral 5-$HT_{2A/2C}$ receptors which may account for its efficacy in resistant cases of schizophrenia.

5. Risperidone This atypical antipsychotic is a combined 5-HT_{2A} + dopamine D2 antagonist, similar to clozapine. Like the latter, it especially ameliorates negative symptoms of schizophrenia, but produces extrapyramidal side effects at only slightly higher doses.

Other atypical antipsychotics like *olanzapine* and *quetiapine* are also combined 5-HT and DA antagonists, but interact with other neurotransmitter receptors as well.

6. Ondansetron It is the prototype of the new class of selective 5-HT_3 antagonists that have shown remarkable efficacy in controlling nausea and vomiting following administration of highly emetic anticancer drugs and radiotherapy. It is described in Ch. 47.

Granisetron and *Tropisetron* are the other selective 5-HT_3 antagonists.

ERGOT ALKALOIDS

Ergot is a fungus *Claviceps purpurea* which grows on rye, millet and some other grains. The grain is replaced by a purple, hard, curved body called 'sclerotium'. Epidemics of ergot poisoning (ergotism), due to consumption of contaminated grains, have been recorded from the beginning of history. It still occurs in epidemic and sporadic forms. Dry gangrene of hands and feet which become black (as if burnt) is the most prominent feature. Miscarriages occur in women and cattle. A convulsive type is also described.

Ergot had been used by midwives to quicken labour since the middle ages. This use received medical sanction in the 19th century, but its dangers were recognized by the beginning of the 20th century and then it was advocated only after delivery. Dale and Barger (1906 onwards) isolated the ergot alkaloids and studied their pharmacology. Ergometrine was isolated in 1935.

Ergot contains a host of pharmacologically active substances—alkaloids, LSD, histamine, ACh, tyramine and other amines, sterols, etc.

Natural ergot alkaloids

These are tetracyclic indole containing compounds which may be considered as derivatives of *lysergic acid*. They are divided into—

(a) *Amine alkaloid* Ergometrine (Ergonovine): which is oxytocic

(b) *Amino acid alkaloids* Ergotamine, Ergotoxine (mixture of ergocristine + ergocornine + ergocryptine): they are vasoconstrictor and α adrenergic blocker/partial agonist.

Other semisynthetic derivatives

(a) Dihydroergotamine (DHE), Dihydroergotoxine (Codergocrine): are antiadrenergic, cerebroactive.

(b) 2-Bromo-α-ergocryptine (Bromocriptine): is a dopaminergic D2 agonist (*see* Ch. 17).

(c) Methysergide: it is mainly anti 5-HT.

The ergot alkaloid related compounds have diverse pharmacological properties. They act as agonists, partial agonists and antagonists on certain subtypes of a adrenergic, serotonergic and dopaminergic receptors in a tissue specific manner.

Actions

Ergotamine It acts as a partial agonist and antagonist at α adrenergic and all subtypes of 5-HT_1 and 5-HT_2 receptors, but does not interact with 5-HT_3 or dopamine receptors: produces

sustained vasoconstriction, visceral smooth muscle contraction, vasomotor centre depression and antagonizes the action of NA and 5-HT on smooth muscles. The overall effect of oral/rectal doses of ergotamine on BP is insignificant. It is a potent emetic (through CTZ and vomiting centre) and moderately potent oxytocic. At high doses CNS stimulation and paresthesias may be experienced. On chronic exposure (ergot poisoning) vasoconstriction is accompanied by damage to capillary endothelium—thrombosis, vascular stasis and gangrene.

Dihydroergotamine (DHE) Hydrogenation of ergotamine reduces serotonergic and α-adrenergic agonistic actions, but enhances α-receptor blocking property. Consequently DHE is a less potent vasoconstrictor; primarily constricts capacitance vessels and causes less intimal damage. It is a weaker emetic and oxytocic, but has some antidopaminergic action as well.

Dihydroergotoxine (Codergocrine) This hydrogenated mixture of ergotoxine group of alkaloids is a more potent α blocker and a very weak vasoconstrictor. In the brain, a variety of partial agonistic/antagonistic actions on 5-HT receptors, metabolic and vascular effects and enhancement of ACh release in cerebral cortex have been demonstrated. It has been advocated for treatment of dementia (*see* Ch. 35).

Bromocriptine The 2 bromo derivative of ergocryptine is a relatively selective dopamine D2 agonist on pituitary lactotropes (inhibits prolactin release), in striatum (antiparkinsonian) and in CTZ (emetic—but less than ergotamine). In certain brain areas weak antidopaminergic action has also been shown. It has very weak anti 5-HT or α blocking actions and is not an oxytocic.

Ergometrine (Ergonovine) This amine ergot alkaloid has very weak agonistic and practically no antagonistic action on α adrenergic receptors: vasoconstriction is not significant. Partial agonistic action on 5-HT receptors has been demonstrated in uterus, placental and umbilical blood vessels and in certain brain areas. It is a moderately potent 5-HT_2 antagonist in g.i. smooth muscle and a weak dopaminergic agonist on the pituitary lactotropes as well as CTZ; emetic potential is low. The most prominent action is contraction of myometrium; used exclusively in obstetrics (*see* Ch. 23).

Pharmacokinetics Oral bioavailability of amino acid ergot alkaloids and their hydrogenated derivatives is poor (< 1%) due to slow and incomplete absorption as well as high firstpass metabolism. Bioavailability is better after sublingual and rectal administration, but still often erratic. They are metabolized in liver and excreted primarily in bile. Ergotamine is sequestrated in tissues—produces longer lasting actions compared to its plasma t½ of 2 hours. Ergot alkaloids effectively cross blood-brain barrier.

Adverse effects Nausea, vomiting, abdominal pain, muscle cramps, weakness, paresthesias, coronary and other vascular spasm, chest pain (due to coronary vasoconstriction) are the frequent side effects. These drugs are contraindicated in presence of sepsis, ischaemic heart disease, peripheral vascular disease, hypertension, pregnancy, liver and kidney disease.

Preparations and dose

Ergotamine: For migraine 1–3 mg oral/sublingual, repeat as required (max 6 mg in a day); rarely 0.25–0.5 mg i.m. or s.c.; ERGOTAMINE 1 mg tab, 0.5 mg/ml inj.
Dihydroergotamine: For migraine 2–6 mg oral (max 10 mg/day), 0.5–1 mg i.m., s.c. repeat hourly (max 3 mg); DIHYDERGOT, DHE 1 mg tab, MIGRANIL 1 mg/ml inj. Also used for postural hypotension, herpes zoster, mumps.
Dihydroergotoxine (codergocrine) For dementia 1–1.5 mg oral or sublingual, 0.15–0.6 mg i.m., HYDERGINE 1.5 mg tab, CERELOID 1 mg tab.

DRUG THERAPY OF MIGRAINE

Migraine is a mysterious disorder characterized by pulsating headache, usually restricted to one side, which comes in attacks lasting 4–48 hours and is often associated with nausea, vomiting, sensitivity to light and sound, flashes of light, vertigo, loose motions and other symptoms. Two major types are—*migraine with aura* (classical migraine) in which headache is preceded by visual or other neurological symptoms, and *migraine without aura* (common migraine). Pulsatile dilatation of certain large cranial vessels is the immediate cause of pain. The pathogenic mechanisms are not well

understood. The *Vascular theory* holds that initial vasoconstriction or shunting of blood through carotid arteriovenous anastomoses produces cerebral ischaemia and starts the attack. The *Neurogenic theory* considers it to be a spreading depression of cortical electrical activity followed by vascular phenomena. Some triggering event appears to produce neurogenic inflammation of the affected blood vessel wall which is amplified by retrograde transmission in the afferent nerves and release of mediators like 5-HT, neurokinin, substance P, calcitonin gene related peptide (CGRP), nitric oxide, etc.

Changes in blood/urinary levels of 5-HT and its metabolites during migraine attack, its precipitation by 5-HT releasers and efficacy of drugs having actions in the serotonergic system to prevent/abort/terminate migraine attacks suggests a pivotal role of 5-HT in this disorder.

Drug therapy of migraine has to be individualized: severity and frequency of attacks and response of individual patients to drugs used earlier determine the choice. The strategy mostly adopted is summarized in the box.

Mild migraine Cases having fewer than one attack per month of throbbing but tolerable headache lasting upto 8 hours which does not incapacitate the individual may be classified as mild migraine.

(i) *Simple analgesics* like paracetamol (0.5–1 g) or aspirin (300–600 mg) taken at the first indication of an attack and repeated 4–6 hourly abort and suppress most mild attacks.

(ii) *Nonsteroidal antiinflammatory drugs (NSAIDs) and their combinations* Drugs like ibuprofen (400–800 mg 8 hourly), naproxen (500 mg followed by 250 mg 8 hourly), diclofenac (50 mg 8 hourly), mephenamic acid (500 mg 8 hourly), indomethacin (50 mg 6–8 hourly) either alone or combined with paracetamol/codeine/diazepam or another sedative/diphenhydramine or another antihistaminic/caffeine are found more satisfactory by some patients. These drugs are more effective in migraine without aura, but certain patients of migraine with aura also prefer them over specific antimigraine drugs (triptans/ergot alkaloids). Drugs are taken only till the attack passes off. Taken in the prodromal stage they can also abort an attack, but long-term treatment on a regular schedule to ward off migraine attacks is not advised.

(iii) *Antiemetics* Gastric stasis occurs during migraine which delays absorption of oral drugs. Metoclopramide (10 mg oral/i.m.) is frequently used: relieves nausea, vomiting and gastric stasis. When the patient has already vomited, it is better to give the antiemetic by injection. Domperidone (10–20 mg oral) and prochlorperazine (10–25 mg oral/i.m.) are also effective. Diphenhydramine or promethazine exert sedative as well as antiemetic action.

Drug therapy of migraine

Severity	*Drug therapy*
Mild	: Simple analgesics/NSAIDs or their combinations (± antiemetic)
Moderate	: NSAIDs combinations/a triptan/ergot alkaloids (+ antiemetic)
Severe	: a Triptan/ergot alkaloids (+ antiemetic) + Prophylaxis • Propranolol/other β blockers • Amitriptyline/other tricyclic antidepressants • Flunarizine/other Ca^{2+} channel blockers • Valproate/topiramate

Moderate migraine Migraine may be labelled as moderate when the throbbing headache is more intense, lasts for 6–24 hours, nausea/vomiting and other features are more prominent and the patient is functionally impaired. One or more attacks occur per month.

Simple analgesics are usually not effective, but stronger NSAIDs or their combinations mentioned above are beneficial in many cases. The remaining are treated with a specific antimigraine drug, i.e. a triptan or an ergot preparation. Antiemetics are almost regularly needed. Prophylactic therapy is advised only when attacks are more frequent than 2–3 per month.

Severe migraine These patients suffer 2–3 or more attacks per month of severe throbbing headache lasting 12–48 hours, often accompanied by vertigo, vomiting and other symptoms; the subject is grossly incapacitated during the attack.

Analgesics/NSAIDs and their combinations usually donot afford adequate relief—specific drugs have to be prescribed along with antiemetics.

Prophylactic regimens lasting 6 months or more are recommended.

SPECIFIC ANTIMIGRAINE DRUGS

Ergotamine It is the most effective ergot alkaloid for migraine. Given early in attack, relief is often dramatic and lower doses suffice, but when pain has become severe—larger doses are needed and control may be achieved only after few hours. Oral/sublingual route is preferred, 1 mg is given at half hour intervals till relief is obtained or a total of 6 mg is given. Parenteral administration, though rapid in action is more hazardous.

Ergotamine acts by constricting the dilated cranial vessels and/or by specific constriction of carotid A-V shunt channels. Ergotamine and DHE have also been shown to reduce neurogenic inflammation and leakage of plasma in duramater that occurs due to retrograde stimulation of perivascular afferent nerves. These actions appear to be mediated through partial agonism at $5\text{-HT}_{1D/1B}$ receptors in and around cranial vessels.

Dihydroergotamine (DHE) It is nearly as effective as ergotamine and preferred for parenteral administration because injected DHE is less hazardous.

Current status Because of erratic oral absorption, frequent side effects, especially nausea and vomiting, and availability of triptans, ergot preparations are rarely used now, except for considerations of cost or when triptans fail. Ergot alkaloids have no prophylactic value: regular use is not justified—may itself produce a dull background headache and an attack may be precipitated on discontinuation. *Caffeine* 100 mg taken with ergotamine enhances its absorption from oral and rectal routes and adds to the cranial vasoconstricting action. Many combination preparations are available.

MIGRIL: Ergotamine 2 mg, caffeine 100 mg, cyclizine 50 mg tab.

VASOGRAIN: Ergotamine 1 mg, caffeine 100 mg, paracetamol 250 mg, prochlorperazine 2.5 mg tab.

Selective $5\text{-HT}_{1D/1B}$ agonists (Triptans)

This novel class of antimigraine drugs selectively activate $5\text{-HT}_{1D/1B}$ receptors, and are called 'triptans'. Currently, they are the first line drugs for patients who fail to respond to analgesics. Ergot alkaloids are now required only in few cases. Because these drugs have been designed to act on the same subtype of 5-HT receptor, pharmacodynamic differences among them are minor, but there are significant pharmacokinetic differences. All others have higher oral bioavailability than the prototype drug sumatriptan. Fewer headache recurrences in an attack are reported with naratriptan and frovatriptan due to their longer t½, but they may be slower in affording initial pain relief.

Sumatriptan It is the first selective $5\text{-HT}_{1D/1B}$ receptor agonist; activates other subtypes of 5-HT_1 receptors only at very high concentrations, and does not interact with 5-HT_2, 5-HT_3, $5\text{-HT}_{4\text{-}7}$, α or β adrenergic, dopaminergic, cholinergic or GABA receptors. Administered at the onset of an attack of migraine, sumatriptan is as effective and better tolerated than ergotamine. About 3/4 patients obtain complete/significant relief within 2–3 hours. However, recurrence of headache within 24 hr has been noted in 20–40% patients, probably due to short t½ of sumatriptan. A distinct advantage is that it tends to suppress nausea and vomiting of migraine, while ergotamine accentuates these symptoms.

The antimigraine activity of sumatriptan has been ascribed to $5\text{-HT}_{1D/1B}$ receptor mediated constriction of dilated cranial blood vessels, especially the arterio-venous shunts in the carotid artery, which express $5\text{-HT}_{1D/1B}$ receptors. Dilatation of these shunt vessels during migraine attack is believed to divert blood flow away from brain parenchyma. Consistent with the fact that $5\text{-HT}_{1D/1B}$ receptors are presynaptic autoreceptors, sumatriptan can reduce 5-HT release at these blood vessels. Alternatively or in addition, it may inhibit inflammatory neuropeptide release around the affected vessels as well as extravasation of plasma proteins across dural vessels. Like ergotamine, the triptans have been found to

suppress neurogenic inflammation of cranial vessels. The use of sumatriptan (or other triptans) should be restricted to treatment of acute attacks of moderate to severe migraine not responding to analgesics or their combinations.

Pharmacokinetics: Sumatriptan is absorbed rapidly and completely after s.c. injection. Oral bioavailability averages only 15%. Absorption is faster after intranasal spray, but bioavailability remains almost the same. It is rapidly metabolized by MAO-A isoenzyme and metabolites are excreted in urine; elimination t½ is ~2 hours.

Side effects: to sumatriptan are usually mild. Tightness in head and chest, feeling of heat and other paresthesias in limbs, dizziness, weakness are short lasting, but dose related side effects. These are more common after s.c. injection, which is painful. Slight rise in BP occurs, but has little clinical relevance, because sumatriptan is not a drug for regular use. Bradycardia, coronary vasospasm and risk of myocardial infarction are the serious, but infrequent adverse effects. Few sudden deaths have been ascribed to sumatriptan. Seizures and hypersensitivity reactions are rare.

Contraindications: Ischaemic heart disease, hypertension, epilepsy, hepatic or renal impairment and pregnancy are the contraindications. Patients should be cautioned not to drive.

Sumatriptan and ergotamine should not be administered within 24 hours of each other. Interaction with 5-HT reuptake inhibitors, MAO inhibitors and lithium has been reported.

Dose: 50–100 mg oral at the onset of migraine attack, may be repeated once within 24 hours if required. Those not responding to the first dose should not be given the second dose. It is the only triptan available for parenteral use; 6 mg s.c. may be given to patients who cannot take the drug orally or in whom the pain develops very rapidly. After injection, it acts in 10–20 min and is more consistently effective. Alternatively, for rapid action and in patients who vomit out the oral tablet, 25 mg nasal spray can be used. It may be repeated once after 2 hours. A bitter taste may be felt after the nasal spray.

MIGRATAN, 50, 100 mg tabs, SUMINAT 25, 50, 100 mg tab, 25 mg nasal spray, 6 mg/0.5 ml inj. SUMITREX 25, 50, 100 mg tab, 6 mg/0.5 ml inj.

Rizatriptan: This congener of sumatriptan is more potent, has higher oral bioavailability with slightly faster onset of action.

Dose: 5-10 mg; repeat once after 2 hr (if required).

RIZACT, RIZATAN 5, 10 mg tab.

Naratriptan, Zolmitriptan, Almotriptan, Frovatriptan and *Eletriptan* are other triptans used in some countries.

Features of some triptans are compared in the box.

PROPHYLAXIS OF MIGRAINE

Regular medication to reduce the frequency and/or severity of attacks is recommended for moderate-to-severe migraine when 2–3 or more attacks occur per month. Diverse classes of drugs are used but none is effective in all cases, and none abolishes the attacks totally. It may be prudent to discontinue pophylaxis every 6 months to check whether its continuation is needed or not. It is important to avoid the precipitating factor(s).

(i) *β-Adrenergic blockers* Propranolol is the most commonly used drug: reduces frequency as well as severity of attacks in upto 70% patients. Effect is generally seen in 4 weeks and is sustained during prolonged therapy. The starting dose is 40 mg BD, which may be increased upto

Comparative features of triptans

	Suma.	*Frova.*	*Riza.*	*Nara.*	*Zolmi.*
1. Oral bioavailability (%)	15	25	45	70	40
2. T*max** (hr)	1.5–2	2–4	1–1.5	2–3	1.5–2
3. Plasma t½ (hr)	~2	26	2–3	6	2–3
4. Oral dose					
Initial (mg)	50–100	2.5	5–10	2.5	2.5
Max. in 24 hr (mg)	200	5–7.5	20	5	10

* T*max*: Time to peak plasma concentration after oral dosing.

160 mg BD if required. The mechanism of action is not clear; that it is due to β adrenergic blockade has been questioned. Other nonselective (timolol) and β_1 selective (metoprolol, atenolol) agents are also effective, but pindolol and others having intrinsic sympathomimetic action are not useful.

(ii) *Tricyclic antidepressants* Many tricyclic compounds of which amitriptyline (25–50 mg at bed time) has been most extensively tried, reduce migraine attacks. It is effective in many patients but produces more side effects than propranolol. It is not known whether its 5-HT (and other monoamine) uptake blocking property is causally related to the prophylactic effect. The antimigraine effect is independent of antidepressant property, but this class of drugs are better suited for patients who also suffer from depression.

(iii) *Calcium channel blockers* Verapamil was found to reduce migraine attacks, but was judged inferior to propranolol. *Flunarizine* is a relatively weak Ca^{2+} channel blocker that also inhibits Na^{+} channels. It is claimed to be as effective as propranolol, but convincing proof is lacking. Frequency of attacks is often reduced, but effect on intensity and duration of attacks is less well documented. It is claimed to be a cerebro-selective Ca^{2+} channel blocker; may benefit migraine by reducing intracellular Ca^{2+} overload due to brain hypoxia and other causes. Side effects are sedation, constipation, dry mouth, hypotension, flushing, weight gain and rarely extrapyramidal symptoms.

Dose: Flunarizine 10–20 mg OD, children 5 mg OD, NOMIGRAIN, FLUNARIN 5 mg, 10 mg caps/tab.

(iv) Anticonvulsants Valproic acid (400–1200 mg/day) and gabapentin (300–1200 mg/day) have some prophylactic effect in migraine. The newer drug topiramate has recently been approved for migrain prophylaxis. A 50% reduction in the number of attacks in half of the patients was noted in 2 randomized trials. Start with topiramate 25 mg OD and gradually increase to 50 mg OD or BD. Efficacy of anticonvulsants in migraine is lower than that of β blockers. They are indicated in patients refractory to other drugs or when propranolol is contraindicated.

(v) 5-HT antagonists The prophylactic effect of methysergide and cyproheptadine is less impressive than β blockers. They are seldom used now for migraine.

Chapter 13 Prostaglandins, Leukotrienes (Eicosanoids) and Platelet Activating Factor

PROSTAGLANDINS AND LEUKOTRIENES (Eicosanoids)

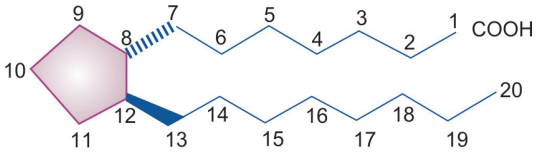
Prostaglandins (PGs) and Leukotrienes (LTs) are biologically active derivatives of 20 carbon atom polyunsaturated essential fatty acids that are released from cell membrane phospholipids. They are the major lipid derived autacoids.

In the 1930s human semen was found to contract isolated uterine and other smooth muscle strips and to cause fall in BP in animals. The active principle was termed 'prostaglandin', thinking that it was derived from prostate. Only in the 1960s it was shown to be a mixture of closely related compounds, the chemical structures were elucidated and widespread distribution was revealed. In 1970s it became clear that aspirin like drugs act by inhibiting PG synthesis, and that in addition to the classical PGs (Es and Fs), thromboxane (TX), prostacyclin (PGI) and leukotrienes (LTs) were of great biological importance. Bergstrom, Samuelsson and Vane got the Nobel prize in 1982 for their work on PGs and LTs. Over the past 40 years they have been among the most intensely investigated substances.

CHEMISTRY, BIOSYNTHESIS AND DEGRADATION

Chemically, PGs may be considered to be derivatives of *prostanoic acid,* though prostanoic acid does not naturally occur in the body. It has a five membered ring and two side chains projecting in opposite directions at right angle to the plane of the ring. There are many series of PGs and thromboxanes (TXs) designated A, B, C....I, depending on the ring structure and the substituents on it. Each series has members with subscript 1, 2, 3 indicating the number of double bonds in the side chains.

Leukotrienes are so named because they were first obtained from leukocytes (*leuko*) and have 3 conjugated double bonds (*triene*). They have also been similarly designated A, B, C.....F and given subscripts 1, 2, 3, 4.



PROSTANOIC ACID

In the body PGs, TXs and LTs are all derived from eicosa (referring to 20 C atoms) tri/tetra/penta enoic acids. Therefore, they can be collectively called *eicosanoids.* In human tissues, the fatty acid released from membrane lipids in largest quantity is *5,8,11,14 eicosa tetraenoic acid (arachidonic acid).* During PG, TX and prostacyclin synthesis, 2 of the 4 double bonds of arachidonic acid get saturated in the process of cyclization, leaving 2 double bonds in the side chain. Thus, subscript 2 PGs are the most important in man, e.g. PGE_2, $PGF_{2\alpha}$, PGI_2, TXA_2. No cyclization or reduction of double bonds occurs during LT synthesis—the LTs of biological importance are LTB_4, LTC_4, LTD_4.

Eicosanoids are the most universally distributed autacoids in the body. Practically every cell and tissue is capable of synthesizing one or more types of PGs or LTs. The pathways of biosynthesis of eicosanoids are summarized in Fig. 13.1.

There are no preformed stores of PGs and LTs. They are synthesized locally and the rate of synthesis is governed by the rate of release of arachidonic acid from membrane lipids in response to appropriate stimuli. These stimuli activate hydrolases, including phospholipase A, probably through increased intracellular Ca^{2+}.

The *cyclooxygenase* (COX) pathway generates eicosanoids with a ring structure (PGs, TXs, prostacyclin) while *lipoxygenase* (LOX) produces open chain compounds (LTs). All tissues have COX—can form cyclic endoperoxides PGG_2 and

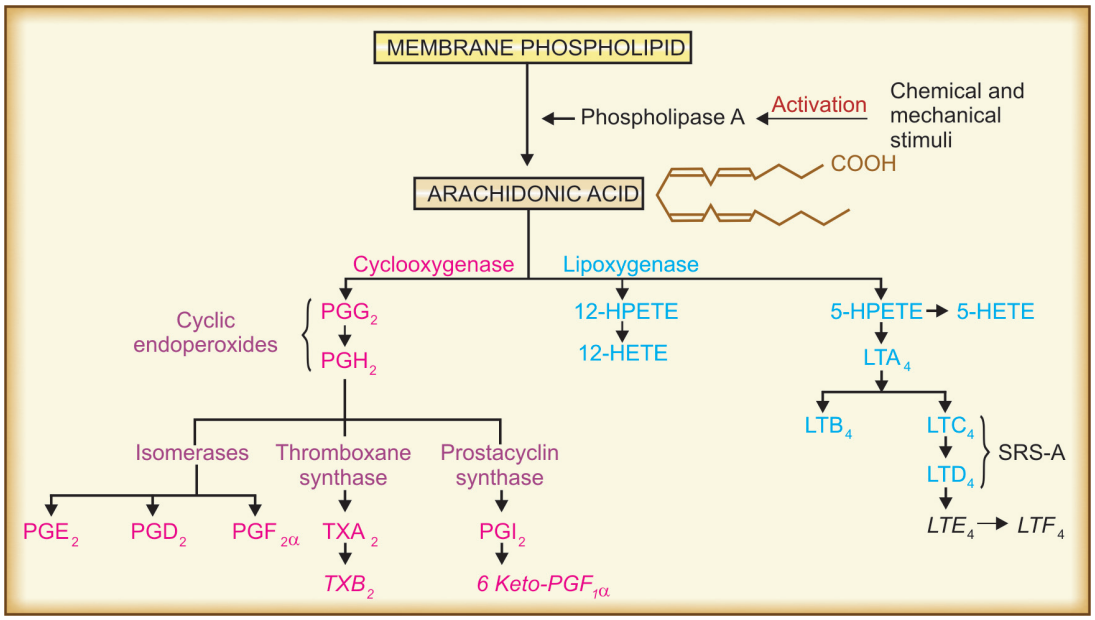


Fig. 13.1: Biosynthesis of prostaglandins (PG) and leukotrienes (LT). Less active metabolites are shown in italics TX—Thromboxane, PGI—Prostacyclin; HPETE—Hydroperoxy eicosatetraenoic acid (Hydroperoxy arachidonic acid); HETE—Hydroxyeicosatetraenoic acid (Hydroxy arachidonic acid); SRS-A—Slow reacting substance of anaphylaxis

PGH_2 which are unstable compounds. Further course in a particular tissue depends on the type of isomerases or other enzymes present in it. PGE_2 and $PGF_{2\alpha}$ are the primary prostaglandins (name based on the separation procedure: PGE partitioned into *Ether* while PGF into phosphate [*Fosfat* in Swedish] buffer; α in $PGF_{2\alpha}$ refers to orientation of OH group on the ring). PGs A, B and C are not found in the body: they are artifacts formed during extraction procedures. Lung and spleen can synthesize the whole range of COX products. Platelets primarily synthesize TXA_2 which is—chemically unstable, spontaneously changes to TXB_2. Endothelium mainly generates prostacyclin (PGI_2) which is also chemically unstable and rapidly converts to 6-keto $PGF_{1\alpha}$.

Cyclooxygenase is known to exist in two isoforms COX-1 and COX-2. While both isoforms catalyse the same reactions, COX-1 is a constitutive enzyme in most cells—it is synthesized and is active in the basal state; the level of COX-1 activity is not much changed once the cell is fully grown. On the other hand, COX-2 normally present in insignificant amounts, is inducible by cytokines, growth factors and other stimuli during the inflammatory response. It is believed that eicosanoids produced by COX-1 participate in physiological (house keeping) functions such as secretion of mucus for protection of gastric mucosa, haemostasis and maintenance of renal function, while those produced by COX-2 lead to inflammatory and other pathological changes. However, certain sites in kidney, brain and the foetus constitutively express COX-2 which may play physiological role.

A splice variant of COX-1 (designated COX-3) has been found in the dog brain. This isoenzyme is inhibited by paracetamol and is implicated in the genesis of fever, but the exact role in humans is not known.

Lipoxygenase pathway appears to operate mainly in the lung, WBC and platelets. Its most important products are the LTs, (generated by 5-LOX) particularly LTB_4 (potent chemotactic) and LTC_4, LTD_4 which together constitute the 'slow reacting substance of anaphylaxis' (SRS-A) described in 1938 to be released during anaphylaxis.

A membrane associated transfer protein called FLAP (five lipoxygenase activating protein) carrys arachidonic acid to 5-LOX, and is essential for the synthesis of LTs. Platelets have only 12-LOX.

HPETEs produced by LOX can also be converted to *hepoxilins, trioxilins* and lipoxins. A third enzymatic pathway involving cytochrome P450 can metabolize arachidonic acid into *19-* and *20-HETEs* and *epoxyeicosatrienoic acids*. Free radicals can attack arachidonic acid to produce *isoprostanes* nonenzymatically. Brain cells couple arachidonic acid with ethanolamine to produce *anandamide* and a few other related eicosanoids which are now recognized to be the endogenous cannabinoid receptor ligands, and produce cannabis like effects. Like the other eicosanoids, they are synthesized only when needed at the site of action.

Inhibition of synthesis Synthesis of COX products can be inhibited by nonsteroidal antiinflammatory drugs (NSAIDs). Aspirin acetylates COX at a serine residue and causes irreversible inhibition while other NSAIDs are competitive and reversible inhibitors. Most NSAIDs are nonselective COX-1 and COX-2 inhibitors, but some later ones like celecoxib, etoricoxib are selective for COX-2.

The sensitivity of COX in different tissues to inhibition by these drugs varies; selective inhibition of formation of certain products may be possible at lower doses. NSAIDs do not inhibit the production of LTs: this may even be increased since all the arachidonic acid becomes available to the LOX pathway.

Zileuton inhibits LOX and decreases the production of LTs. It was used briefly in asthma, but has been withdrawn.

Glucocorticosteroids inhibit the release of arachidonic acid from membrane lipids (by stimulating production of proteins called *annexins* which inhibit phospholipase A_2)—indirectly reduce production of all eicosanoids—PGs, TXs and LTs. Moreover, they inhibit the induction of COX-2 by cytokines at the site of inflammation.

Degradation Biotransformation of arachidonates occurs rapidly in most tissues, but fastest in the lungs. Most PGs, TXA_2 and prostacyclin have plasma t½ of a few seconds to a few minutes. First a specific carrier mediated uptake into cells occurs, the side chains are then oxidized and double bonds are reduced in a stepwise manner to yield inactive metabolites. Metabolites are excreted in urine. PGI_2 is catabolized mainly in the kidney.

ACTIONS AND PATHOPHYSIOLOGICAL ROLES

Prostaglandins, thromboxanes and prostacyclin

The cyclic eicosanoids produce a wide variety of actions depending upon the particular PG (or TX or PGI), species on which tested, tissue, hormonal status and other factors. PGs differ in their potency to produce a given action and different PGs sometimes have opposite effects. Even the same PG may have opposite effects under different circumstances. The actions of PGs and TXA_2 are summarized in Table 13.1. Since virtually all cells and tissues are capable of forming one or more PGs, these autacoids have been implicated as mediators or modulators of a number of physiological processes and pathological states.

1. CVS PGE_2 and $PGF_{2\alpha}$ cause vasodilatation in most, but not all, vascular beds. In isolated preparations, they are more potent vasodilators than ACh or histamine. $PGF_{2\alpha}$ constricts many larger veins including pulmonary vein and artery. Fall in BP occurs when PGE_2 is injected i.v., but $PGF_{2\alpha}$ has little effect on BP.

- PGI_2 is uniformly vasodilatory and is more potent hypotensive than PGE_2.
- TXA_2 consistently produces vasoconstriction.
- PG endoperoxides (G_2 and H_2) are inherently vasoconstrictor, but often produce vasodilatation or a biphasic response due to rapid conversion to other PGs, especially PGI_2 in the blood vessels themselves.
- PGE_2 and $F_{2\alpha}$ stimulate heart by weak direct but more prominent reflex action due to fall in BP. The cardiac output increases.

Role

(i) PGs do not circulate in blood and have no role in regulating systemic vascular resistance. However, PGI_2 generated in the

vascular endothelium, mainly by COX-2, appears to be involved in the regulation of local vascular tone as a dilator.

(ii) PGE_2 is continuously produced locally in the ductus arteriosus by COX-2 during foetal life—keeps it patent; at birth its synthesis stops and closure occurs. Aspirin and indomethacin induce closure when it fails to occur spontaneously. These PGs may also be important in maintaining placental blood flow.

(iii) PGs, generated mainly by COX-2, along with LTs and other autacoids may mediate vasodilatation and exudation at the site of inflammation.

2. Platelets TXA_2, which can be produced locally by platelets, is a potent inducer of aggregation and release reaction. The endoperoxides PGG_2 and PGH_2 are also proaggregatory. On the other hand PGI_2 (generated by vascular endothelium) is a potent inhibitor of platelet aggregation. PGD_2 has antiaggregatory action, but much less potent than PGI_2. PGE_2 has dose dependent and inconsistent effects.

Role TXA_2 produced by platelets and PGI_2 produced by vascular endothelium probably constitute a mutually antagonistic system: preventing aggregation of platelets while in circulation and inducing aggregation on injury, when plugging and thrombosis are needed.

Aspirin interferes with haemostasis by inhibiting platelet aggregation. TXA_2 produced by platelet COX-1 plays an important role in amplifying aggregation. Before it is deacetylated in liver, aspirin acetylates COX-1 in platelets while they are in portal circulation. Further, platelets are unable to regenerate fresh COX-1 (lack nucleus: do not synthesize protein), while vessel wall is able to do so (fresh enzyme is synthesized within hours). Thus, in low doses, aspirin selectively inhibits TXA_2 production and has antithrombotic effect lasting > 3 days.

3. Uterus PGE_2 and $PGF_{2\alpha}$ uniformly contract human uterus, *in vivo*, both pregnant as well as nonpregnant. The sensitivity is higher during pregnancy and there is progressive modest increase with the advance of pregnancy. However, even during early stages, uterus is quite sensitive to PGs though not to oxytocin. PGs increase basal tone as well as amplitude of uterine contractions.

When tested *in vitro*, $PGF_{2\alpha}$ consistently produces contraction while PGE_2 relaxes nonpregnant but contracts pregnant human uterine strips.

At term, PGs soften the cervix at low doses and make it more compliant.

Role

(i) Foetal tissues produce PGs. At term $PGF_{2\alpha}$ has been detected in maternal blood. It is postulated that PGs mediate initiation and progression of labour. Aspirin has been found to delay the initiation of labour and also prolong its duration.

(ii) Because PGs are present in high concentration in semen and can be rapidly absorbed when lodged in the vagina at coitus, it is believed that they so coordinate movements of the female genital tract that transport of sperms and fertilization is facilitated.

(iii) Dysmenorrhoea in many women is associated with increased PG synthesis by the endometrium. This apparently induces uncoordinated uterine contractions which compress blood vessels → uterine ischaemia → pain. Aspirin group of drugs are highly effective in relieving dysmenorrhoea in most women.

4. Bronchial muscle $PGF_{2\alpha}$, PGD_2 and TXA_2 are potent bronchoconstrictors (more potent than histamine) while PGE_2 is a powerful bronchodilator. PGI_2 produces mild dilatation. Asthmatics are more sensitive to constrictor as well as dilator effects of PGs. PGE_2 and PGI_2 also inhibit histamine release and are effective by aerosol. However, these antiasthmatic effects of PGE_2 and PGI_2 cannot be exploited clinically because they produce irritation of the respiratory tract and have a brief action.

TABLE 13.1 **A summary of the actions of major prostaglandins, prostacyclin and thromboxane**

	Organ	*Prostaglandin E_2 (PGE_2)*	*Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$)*	*Prostacyclin (PGI_2)*	*Thromboxane A_2 (TXA_2)*
1.	Blood vessels	Vasodilatation, ↓ BP	Vasodilatation (mostly), larger veins constrict, little effect on BP	Vasodilatation (marked and widespread), ↓ ↓ BP	Vasoconstriction
2.	Heart	Weak inotropic, reflex cardiac stimulation	Weak inotropic	—	—
3.	Platelets	Variable effect	—	Antiaggregatory	Aggregation and release reaction
4.	Uterus	Contraction (*in vivo*), relaxes nongravid human uterus *in vitro*, softening of cervix	Contraction (*in vivo* and *in vitro*), softening of cervix	—	—
5.	Bronchi	Dilatation, Inhibit histamine release	Constriction	Dilatation (mild), inhibit histamine release	Constriction
6.	Stomach	↓ acid secretion, ↑ mucus production	—	↓ acid secretion (weak), mucosal vasodilatation	—
7.	Intestine	Contracts longitudinal & relaxes circular muscles, ↑ peristalsis, ↑ Cl^- & water secretion	Spasmogenic, ↑ fluid & electrolyte secretion (weak)	Weak spasmogenic, inhibit toxin-induced fluid secretion	Weak spasmogenic
8.	Kidney	Natriuresis, ↓ Cl^- reabsorption, inhibit ADH action, vasodilatation, renin release	—	Natriuresis, vasodilatation, renin release	Vasoconstriction
9.	CNS	Pyrogenic, variety of effects on i.c.v. inj.			
10.	Release of NA	↑ or ↓	↑ or ↓		
11.	Afferent nerves	Sensitize to noxious stimuli → tenderness	—	Same as PGE_2	—
12.	Endocrine system	Release of ant. pituitary hormones, steroids, insulin; TSH-like action	Release of gonadotropins & prolactin, luteolysis (in animals)	—	—
13.	Metabolism	Antilipolytic, insulin like action, mobilization of bone Ca^{2+}	—	—	—

Role Asthma may be due to an imbalance between constrictor PGs ($F_{2\alpha}$, PGD_2, TXA_2) and LTs on one hand and dilator ones (PGE_2, PGI_2) on the other. In few individuals aspirin-like drugs consistently induce asthma, possibly by diverting arachidonic acid to produce excess LTC_4 and D_4. This sensitivity is not shared by selective COX-2 inhibitors, indicating that suppression of COX-1 at the pulmonary site is responsible for the reaction. In allergic human asthma, LTs play a more important role, and COX inhibitors are without any effect in most patients.

5. GIT (i) In isolated preparations, the longitudinal muscle of gut is contracted by PGE_2 and $PGF_{2\alpha}$ while the circular muscle is either contracted (usually by $PGF_{2\alpha}$) or relaxed (usually by PGE_2). Propulsive activity is enhanced in man, especially by $PGE_2 \rightarrow$ colic and watery diarrhoea are important side effects. PGE_2 acts directly on the intestinal mucosa and increases water, electrolyte and mucus secretion. PGI_2 does not produce diarrhoea and infact opposes PGE_2 and toxin induced fluid movement.

Role PGs may be involved in mediating toxin induced increased fluid movement in secretory diarrhoeas. In certain diarrhoeas, aspirin can reduce stool volume, but is not uniformly effective. PGs appear to play a role in the growth of colonic polyps and cancer. Association of lower incidence of colon cancer with regular intake of aspirin is now established. NSAIDs afford relief in familial colonic polyposis by reducing polyp formation.

(ii) PGE_2 markedly reduces acid secretion in the stomach. Volume of juice and pepsin content are also decreased. It inhibits fasting as well as stimulated secretion (by feeding, histamine, gastrin). Release of gastrin is suppressed (*see* Fig. 46.1). The gastric pH may rise upto 7.0. PGI_2 also inhibits gastric secretion, but is less potent. Secretion of mucus and HCO_3^- by gastric mucosal epithelial cells as well as mucosal blood flow are increased. Thus, PGs are antiulcerogenic.

Role PGs (especially PGI_2) appear to be involved in the regulation of gastric mucosal blood flow. They may be functioning as natural ulcer protectives by enhancing gastric mucus and HCO_3^- production, as well as by improving mucosal circulation and health. The ulcerogenic action of NSAIDs may be due to loss of this protective influence.

Normally, gastric mucosal PGs are produced by COX-1. Selective COX-2 inhibitors are less ulcerogenic. However, COX-2 gets induced during ulcer healing, and COX-2 inhibitors have the potential to delay healing.

6. Kidney PGE_2 and PGI_2 increase water, Na^+ and K^+ excretion and have a diuretic effect. PGE_2 has been shown to have a furosemide-like inhibitory effect on Cl^- reabsorption as well. They cause renal vasodilatation and inhibit tubular reabsorption. PGE_2 antagonizes ADH action, and this adds to the diuretic effect. In contrast, TXA_2 causes renal vasoconstriction. PGI_2, PGE_2 and PGD_2 evoke release of renin.

Role

(i) PGE_2 and PGI_2 produced mainly by COX-2 in the kidney appear to function as intrarenal regulators of blood flow as well as tubular reabsorption in kidney. Accordingly, the NSAIDs, including selective COX-2 inhibitors, tend to retain salt and water. The diuretic action of furosemide is blunted by indomethacin—indicating a facilitatory role of PGs by increasing renal blood flow and/or augmenting inhibition of tubular reabsorption.

(ii) Renin release in response to sympathetic stimulation and other influences may be facilitated by PGs.

(iii) Bartter's syndrome, characterized by decreased sensitivity to angiotensin II is associated with increased PG production; many of the manifestations are improved by prolonged use of NSAIDs.

7. CNS PGs injected i.v. penetrate brain poorly, so that central actions are not prominent. However, injected intracerebroventricularly PGE_2 produces a variety of effects—sedation, rigidity, behavioral changes and marked rise in body temperature. PGI_2 also induces fever, but TXA_2 is not pyrogenic.

Role

(i) PGE_2 may mediate pyrogen induced fever and malaise. Aspirin and other inhibitors of PG synthesis are antipyretic. Pyrogens, including cytokines released during bacterial infection, trigger synthesis of PGE_2 in the hypothalamus, which resets the thermostat to cause fever. COX-2 is the major isoenzyme involved; selective COX-2 inhibitors are equally efficacious antipyretics. A role of COX-3 has also been proposed.

(ii) PGs may be functioning as neuromodulators in the brain by regulating neuronal excitability. A role in pain perception, sleep and some other functions has been suggested.

8. ANS Depending on the PG, species and tissue, both inhibition as well as augmentation of NA release from adrenergic nerve endings has been observed.

Role PGs may modulate sympathetic neurotransmission in the periphery.

9. Peripheral nerves PGs (especially E_2 and I_2) sensitize afferent nerve endings to pain inducing chemical and mechanical stimuli (Fig. 13.2). They irritate mucous membranes and produce long lasting dull pain on intradermal injection.

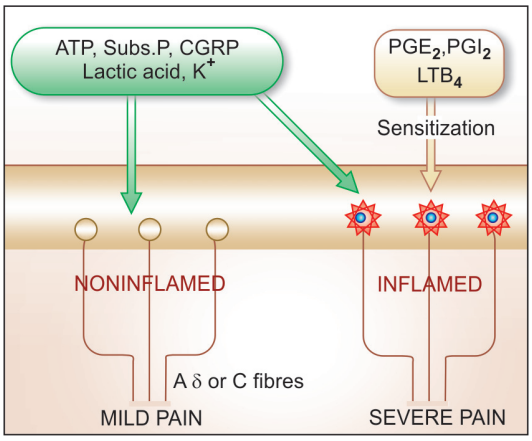


Fig. 13.2: Sensitization of nociceptors (pain receptors) to mediators of pain by prostaglandins at the inflammatory site. Subs. P—Substance P; CGRP—Calcitonin gene related peptide

Role PGs appear to serve as algesic agents during inflammation. They cause tenderness and amplify the action of other algesics. Inhibition of PG synthesis is a major antiinflammatory mechanism. Aspirin injected locally decreases pain produced by injection of bradykinin at the same site.

10. Eye: $PGF_{2\alpha}$ induces ocular inflammation and lowers i.o.t by enhancing uveoscleral and trabecular outflow. Non irritating congeners like *latanoprost* are now first line drugs in wide angle glaucoma.

Role Locally produced PGs appear to facilitate aqueous humor drainage. The finding that COX-2 expression in the ciliary body is deficient in wide angle glaucoma patients supports this cotention.

11. Endocrine system PGE_2 facilitates the release of anterior pituitary hormones—growth hormone, prolactin, ACTH, FSH and LH as well as that of insulin and adrenal steroids. It has a TSH-like effect on the thyroid.

$PGF_{2\alpha}$ causes luteolysis and terminates early pregnancy in many mammals, but this effect is not significant in humans. Though PGs can terminate early pregnancy in women, this is not associated with fall in progesterone levels.

12. Metabolism PGEs are antilipolytic, exert an insulin like effect on carbohydrate metabolism and mobilize Ca^{2+} from bone. They may mediate hypercalcaemia due to bony metastasis.

Leukotrienes

The straight chain lipoxygenase products of arachidonic acid are produced by a more limited number of tissues (LTB_4 mainly by neutrophils; LTC_4 and LTD_4—the cysteinyl LTs—mainly by macrophages), but probably they are pathophysiologically as important as PGs.

1. CVS and blood LTC_4 and LTD_4 injected i.v. evoke a brief rise in BP followed by a more prolonged fall. The fall in BP is not due to vasodilatation because no relaxant action has been

seen on blood vessels. It is probably a result of coronary constriction induced decrease in cardiac output and reduction in circulating volume due to increased capillary permeability. These LTs markedly increase capillary permeability and are more potent than histamine in causing local edema formation. LTB_4 is highly chemotactic for neutrophils and monocytes; this property is shared by HETE but not by other LTs. Migration of neutrophils through capillaries and their clumping at sites of inflammation in tissues is also promoted by LTB_4. The cysteinyl LTs (C_4, D_4) are chemotactic for eosinophils.

Role LTs are important mediators of inflammation. They are produced (along with PGs) locally at the site of injury. While LTC_4 and D_4 cause exudation of plasma, LTB_4 attracts the inflammatory cells which reinforce the reaction. 5-HPETE and 5-HETE may facilitate local release of histamine from mast cells.

2. Smooth muscle LTC_4 and D_4 contract most smooth muscles. They are potent bronchoconstrictors and induce spastic contraction of g.i.t. at low concentrations.

They also increase mucus secretion in the airways.

Role The cysteinyl LTs (C_4 and D_4) are the most important mediators of human allergic asthma. They are released along with PGs and other autacoids during AG: AB reaction in the lungs. In comparison to other mediators, they are more potent and are metabolized slowly in the lungs, exert a long lasting action. LTs may also be responsible for abdominal colics during systemic anaphylaxis.

3. Afferent nerves Like PGE_2 and I_2, the LTB_4 also sensitizes afferents carrying pain impulses—contributes to pain and tenderness of inflammation.

PROSTANOID RECEPTORS

PGs, TX and prostacyclin act on their own specific receptors located on cell membrane. Five families of prostanoid receptors have been designated, each after the natural PG for which it has the greatest affinity. This has been supported by receptor cloning. All prostanoid receptors are G-protein coupled receptors which can be functionally categorized into 'excitatory' or 'contractile' and 'inhibitory' or 'relaxant' groups.

The contractile group (EP_1, FP, TP) couple primarily with Gq protein and activate PLC_β to generate IP_3 and DAG. These second messengers release Ca^{2+} intracellularly resulting in excitatory responses like smooth muscle contraction, platelet aggregation, etc. The relaxant group (DP_1, EP_2, EP_4 and IP) couple with Gs protein—activate adenylyl cyclase to generate intracellular second messenger cAMP. Smooth muscle relaxation, inhibition of platelet aggregation, etc. are produced through cAMP dependent protein kinase (PK_A). The major characteristics of subtypes of prostanoid receptors are:

DP This receptor has strongest affinity for PGD_2, but PGE_2 can also activate it. Two subtypes DP_1 and DP_2 have been identified, but both have limited distribution in the body; DP_1 is a relaxant receptor which dilates certain blood vessels and inhibits platelet aggregation. The DP_2 receptor couples with Gi protein and inhibits cAMP generation.

EP This receptor is characterized by highest affinity for PGE_2; *enprostil* is a selective agonist. Four subtypes have been recognized:

EP_1 is a contactile receptor—contracts visceral smooth muscle, but is less abundant in the body.

EP_2 and EP_4 are relaxant in nature, act by increasing cAMP in smooth muscle, but the same second messenger enhances Cl^- and water secretion by the intestinal mucosa. While EP_2 is present in few organs, EP_4 has wide distribution.

EP_3 is inhibitory, decreases cAMP generation by coupling with Gi protein. The antilipolytic action of PGE_2 is exerted by opposing cAMP generation in adipose tissue. Distribution of PGE_3 receptor in the body is wide.

FP This contactile receptor is highly expressed in the female genital tract, and is present in many other organs. It exhibits strong affinity for $PGF_2\alpha$; *fluprostenol* is a selective agonist.

IP This relaxant receptor is defined by highest affinity for PGI_2, but PGE_2 also acts on it; *cicaprost* is a selective agonist. It is expressed in heart, lungs, kidney, platelet (antiaggregatory), etc., but the highest density is in the vasculature.

TP Characterized by high affinity for TxA_2, this contractile receptor is abundant in platelets (aggregatory), cardiovascular system, immune cells and many other organs. PGH_2 can also activate TP. Apart from IP_3/DAG—Ca^{2+}—PKc pathway, it utilizes other kinases as well to exert certain biological effects.

LEUKOTRIENE RECEPTORS

Separate receptors for LTB_4 (BLT_1 and BLT_2) and for the cysteinyl LTs (LTC_4, LTD_4) have been defined. Two subtypes, *cys*LT_1 and *cys*LT_2 of the cysteinyl LT receptor have been cloned. All LT receptors couple with Gq protein and function through the IP_3/DAG transducer mechanism. The BLT receptors are chemotactic and primarily expressed in leucocytes and spleen. BLT_1 receptor has high, while BLT_2 receptor has lower affinity for LTB_4. The *cys*LT_1 receptor is mainly expressed in bronchial and intestinal muscle and has higher affinity for LTD_4 than for LTC_4. The primary location of *cys*LT_2 receptor is leucocytes and spleen, and it shows no preference for LTD_4 over LTC_4. The *cys*LT_1 receptor antagonists, *viz. Montelukast, Zafirlukast,* etc. are now valuable drugs for bronchial asthma (*see* Ch. 16).

USES

Clinical application of PGs and their analogues is rather restricted because of limited availability, short lasting action, cost and frequent side effects. However, their use in glaucoma and in obstetrics is now common place. Their indications are:

1. *Abortion* During the first trimester, termination of pregnancy by transcervical suction is the procedure of choice. Intravaginal PGE_2 pessary inserted 3 hours before attempting dilatation can minimise trauma to the cervix by reducing resistance to dilatation.

Medical termination of pregnancy of upto 7 weeks has been achieved with high success rate by administering mifepristone (antiprogestin) 600 mg orally 2 days before a single oral dose of misoprostol 400 µg. It is now a valuable alternative to suction-evacuation. Uterine contractions are provoked and the conceptus is expelled within the next few hours. Intravaginal misoprostol is now favoured by many as it produces fewer side effects. Sublingual route is also advocated by some experts. Ectopic pregnancy should be ruled out beforehand and complete expulsion should be confirmed afterwards. Uterine cramps, vaginal bleeding, nausea, vomiting and diarrhoea are the common side effects. Methotrexate administered along with misoprostol is also highly successful for inducing abortion in the first few weeks of pregnancy.

PGs have a place in midterm abortion, missed abortion and molar gestation, though delayed and erratic action and incomplete abortion are a problem. The initial enthusiasm has given way to more considered use. PGs convert the oxytocin resistant midterm uterus to oxytocin responsive one: a single extraamniotic injection (PGE_2) followed by i.v. infusion of oxytocin or intraamniotic ($PGF_{2\alpha}$) with hypertonic solution produces 2nd trimester abortion in a high percentage without undue side effects. Pretreatment with mifepristone improves the efficacy of PGE as abortifacient.

2. *Induction/augmentation of labour* PGs do not offer any advantage over oxytocin for induction of labour at term. They are less reliable and show wider individual variation in action. PGE_2 and $PGF_{2\alpha}$ (rarely) have been used in place of oxytocin in toxaemic and renal failure patients, because PGs do not cause fluid retention that is possible with oxytocin. PGE_2 may also be used to augment labour, if it is slow, in primipara. Intravaginal route is preferred now: side effects care milder; extra/intra amniotic route is infrequently used.

3. *Cervical priming (ripening)* Applied intravaginally or in the cervical canal, low doses of PGE_2 which do not affect uterine motility make the cervix soft and compliant. This procedure has yielded good results in cases with unfavourable cervix. If needed labour may be induced 12 hours later with oxytocin: chances of failure are reduced.

4. *Postpartum haemorrhage (PPH)* Carboprost (15-methyl $PGF_{2\alpha}$) injected i.m. is an alternative drug for control of PPH due to uterine atony, especially in patients unresponsive to ergometrine and oxytocin.

PGE_2 (Dinoprostone) PROSTIN-E_2 for induction/augmentation of labour, midterm abortion.

Vaginal gel (1 mg or 2 mg in 2.5 ml) 1 mg inserted into posterior fornix, followed by 1–2 mg after 6 hour if required.

Vaginal tab (3 mg) 3 mg inserted into posterior fornix, followed by another 3 mg if labour does not start within 6 hour.

Extraamniotic solution (10 mg/ml in 0.5 ml amp.) infrequently used.

Intravenous solution (1 mg/ml in 0.75 ml amp., 10 mg/ml in 0.5 ml amp) i.v. route is rarely used due to more side effects.

Oral tablet PRIMIPROST 0.5 mg tab, one tab. hourly till induction, max 1.5 mg per hr; rarely used.

Cervical gel CERVIPRIME (0.5 mg in 2.5 ml prefilled syringe) 0.5 mg inserted into cervical canal for preinduction cervical softening and dilatation in patients with poor Bishop's score.

Gemeprost CERVAGEM 1 mg vaginal pessary: for softening of cervix in first trimester—1 mg 3 hr before attempting dilatation; for 2nd trimester abortion/molar gestation—1 mg every 3 hours, max. 5 doses.

$PGF_{2\alpha}$ (Dinoprost) PROSTIN F_2 ALPHA intraamniotic injection 5 mg/ml in 4 ml amp. for midterm abortion/induction of labour (rarely used).

15-methyl $PGF_{2\alpha}$ (Carboprost) PROSTODIN 0.25 mg in 1 ml amp; 0.25 mg i.m. every 30–120 min for PPH, midterm abortion, missed abortion.

T-PILL + MISO Mifepristone 200 mg tab (3 tabs) + misoprostol 200 mg (2 tabs); mifepristone 3 tab orally followed 2 days later by misoprostol 2 tab orally, for termination of pregnancy of upto 49 days.

5. *Peptic ulcer* Stable analogue of PGE_1 (misoprostol) is occasionally used for healing peptic ulcer, especially in patients who need continued NSAID therapy or who continue to smoke (*see* Ch. 46).

6. *Glaucoma* Topical $PGF_{2\alpha}$ analogues like *latanoprost, travoprost*, *bimatoprost* that are FP receptor agonists are the first choice drugs in wide angle glaucoma (*see* p. 155).

7. *To maintain patency of ductus arteriosus* in neonates with congenital heart defects, till surgery is undertaken. PGE_1 (Alprostadil) is used; apnoea occurs in few cases.

PROSTIN VR, BIOGLANDIN 0.5 mg in 1 ml amp; dilute and infuse i.v.

8. *To avoid platelet damage* PGI_2 (Epoprostenol) can be used to prevent platelet aggregation and damage during haemodialysis or cardiopulmonary bypass. It also improves harvest of platelets for transfusion.

Few cases of primary *pulmonary hypertension* have been successfully maintained on epoprostenol infusion.

FLOLAN 0.5 mg vial for reconstitution.

The other suggested uses of PGs are:

1. ***Peripheral vascular diseases*** PGI_2 (or PGE_1) infused i.v. can relieve rest pain and promote healing of ischaemic ulcers in severe cases of intermittent claudication and in Raynaud's disease.

2. ***Impotence*** Alprostadil (PGE_1) injected into the penis causes erection lasting 1–2 hours. However, oral sildenafil/tadalafil is now preferred for erectile dysfunction.

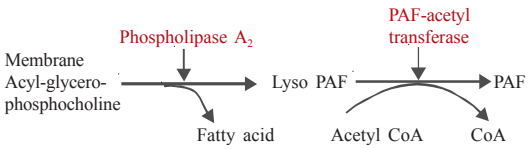
SIDE EFFECTS

Side effects are common in the use of PGs, but their intensity varies with the PG, the dose and the route. These are: nausea, vomiting, watery diarrhoea, uterine cramps, unduly forceful uterine contractions, vaginal bleeding, flushing, shivering, fever, malaise, fall in BP, tachycardia, chest pain.

PLATELET ACTIVATING FACTOR (PAF)

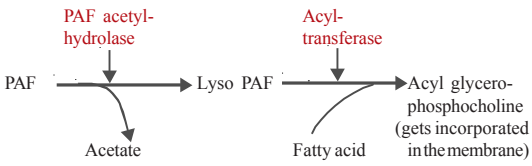
Like eicosanoids, platelet activating factor (PAF) is a cell membrane derived polar lipid with intense biological activity. Discovered in 1970s PAF is active at subnanomolar concentration and is now recognized to be an important signal molecule. PAF is acetyl-glyceryl ether-phosphoryl choline. The ether-linked alkyl chain in human PAF is mostly 16 or 18 C long.

Synthesis and degradation PAF is synthesized from precursor phospholipids present in cell membrane by the following reactions:



The second step is rate limiting. Antigen-antibody reaction and a variety of mediators stimulate PAF synthesis in a Ca^{2+} dependent manner on demand: there are no preformed stores of PAF. In contrast to eicosanoids, the types of cells which synthesize PAF is quite limited—mainly WBC, platelets, vascular endothelium and kidney cells.

PAF is degraded in the following manner:



Actions PAF has potent actions on many tissues/organs.

Platelets Aggregation and release reaction; also releases TXA_2; i.v. injection of PAF results in intravascular thrombosis.

WBC PAF is a potent chemotactic for neutrophils, eosinophils and monocytes. It stimulates neutrophils to aggregate, to stick to vascular endothelium and migrate across it to the site of infection. It also prompts release of lysosomal enzymes and LTs as well as generation of superoxide radical by the polymorphs. The chemotactic action may be mediated through release of LTB_4. It induces degranulation of eosinophils.

Blood vessels Vasodilatation mediated by release of EDRF occurs → fall in BP on i.v. injection. Decreased coronary blood flow has been observed on intracoronary injection, probably due to formation of platelet aggregates and release of TXA_2.

PAF is the most potent agent known to increase vascular permeability. Wheal and flare occur at the site of intradermal injection.

Injected into the renal artery PAF reduces renal blood flow and Na^+ excretion by direct vasoconstrictor action, but this is partly counteracted by local PG release.

Visceral smooth muscle Contraction occurs by direct action as well as through release of LTC_4, TXA_2 and PGs. Aerosolized PAF is a potent bronchoconstrictor. In addition, it produces mucosal edema, secretion and a delayed and long-lasting bronchial hyper-responsiveness. It also stimulates intestinal and uterine smooth muscle.

Stomach PAF is highly ulcerogenic: erosions and mucosal bleeding occur shortly after i.v. injection of PAF. The gastric smooth muscle contracts.

Mechanism of action Membrane bound specific PAF receptors have been identified. The PAF receptor is a G-protein coupled receptor which exerts most of the actions by coupling with Gq protein and generating intracellular messengers IP_3/DAG → Ca^{2+} release. It can also inhibit adenylyl cyclase by coupling with Gi protein.

As mentioned above, many actions of PAF are mediated/augmented by PGs, TXA_2 and LTs which may be considered its extracellular messengers. PAF also acts intracellularly, especially in the endothelial cells; rise in PAF concentration within the endothelial cells is associated with exposure of neutrophil binding sites on their surface. Similarly, its proaggregatory action involves unmasking of fibrinogen binding sites on the surface of platelets.

PAF antagonists A number of natural and synthetic PAF receptor antagonists have been investigated. Important among these are ginkgolide B (from a Chinese plant), and some structural analogues of PAF. The PAF antagonists have manyfold therapeutic potentials like treatment of stroke, intermittent claudication, sepsis, myocardial infarction, shock, g.i. ulceration, asthma and as contraceptive. Some of them have been tried clinically but none has been found worth marketing. Alprazolam and triazolam antagonize some actions of PAF.

Pathophysiological roles PAF has been implicated in many pathological states and some physiological processes by mediating cell-to-cell interaction. These are:

1. *Inflammation:* Generated by leukocytes at the site of inflammation PAF appears to participate in the causation of vasodilatation, exudation, cellular infiltration and hyperalgesia.
2. *Bronchial asthma:* Along with LTC_4 and LTD_4, PAF appears to play a major role by causing bronchoconstriction, mucosal edema, recruiting eosinophils and provoking secretions. It is unique in producing prolonged airway hyperreactivity, so typical of bronchial asthma patient.
3. *Anaphylactic (and other) shock conditions:* are associated with high circulating PAF levels.
4. *Haemostasis and thrombosis:* PAF may participate by promoting platelet aggregation.
5. *Rupture of mature graafian follicle and implantation:* Early embryos which produce PAF have greater chance of implanting. However, PAF is not essential for reproduction.
6. Ischaemic states of brain, heart and g.i.t., including g.i. ulceration.

☞ PROBLEM DIRECTED STUDY

13.1 A full term primigravida presented with labour pains. On examination the BP was 110/70 mm Hg and she was not anaemic. The presentation was vertex, head was engaged, foetal heart sound was normal, there was no cephalopelvic disproportion, no placenta previa, membranes were intact and uterine contractions were adequate. The labour was allowed to progress under observation. After 8 hours the cervix was still firm and not adequately dilated.

(a) Can some medicaion be used to soften the cervix, help its ripening and facilitate delivery? If so, which drug and route of administration should be used?

(b) Given the above findings, is there any contraindication to the use of such medication?

(see Appendix-1 for solution)

Chapter 14 Nonsteroidal Antiinflammatory Drugs and Antipyretic-Analgesics

All drugs grouped in this class have analgesic, antipyretic and antiinflammatory actions in different measures. In contrast to morphine they do not depress CNS, do not produce physical dependence, have no abuse liability and are weaker analgesics (except for inflammatory pain). They are also called *nonnarcotic, nonopioid* or *aspirin-like* analgesics. They act primarily on peripheral pain mechanisms, but also in the CNS to raise pain threshold. They are more commonly employed and many are over-the-counter drugs.

Willow bark (*Salix alba*) had been used for many centuries. Salicylic acid was prepared by hydrolysis of the bitter glycoside obtained from this plant. *Sodium salicylate* was used for fever and pain in 1875; its great success led to the introduction of acetylsalicylic acid (aspirin) in 1899. *Phenacetin* and *antipyrine* were also produced at that time. The next major advance was the development of phenylbutazone in 1949 having antiinflammatory activity almost comparable to corticosteroids. The term Nonsteroidal Antiinflammatory Drug (NSAID) was coined to designate such drugs. *Indomethacin* was introduced in 1963. A host of compounds heralded by the propionic acid derivative *ibuprofen* have been added since then and cyclooxygenase (COX) inhibition is recognised to be their most important mechanism of action. Subsequently some selective COX-2 inhibitors (celecoxib, etc.) have been added.

The antipyretic-analgesics are chemically diverse, but most are organic acids.

CLASSIFICATION

A. *Nonselective COX inhibitors (traditional NSAIDs)*

1. *Salicylates*: Aspirin.
2. *Propionic acid derivatives*: Ibuprofen, Naproxen, Ketoprofen, Flurbiprofen.
3. *Fenamate*: Mephenamic acid.
4. *Enolic acid derivatives*: Piroxicam, Tenoxicam.
5. *Acetic acid derivatives*: Ketorolac, Indomethacin, Nabumetone.
6. *Pyrazolone derivatives*: Phenylbutazone, Oxyphenbutazone.

B. *Preferential COX-2 inhibitors*

Nimesulide, Diclofenac, Aceclofenac, Meloxicam, Etodolac.

C. *Selective COX-2 inhibitors*

Celecoxib, Etoricoxib, Parecoxib.

D. *Analgesic-antipyretics with poor antiinflammatory action*

1. *Paraaminophenol derivative*: Paracetamol (Acetaminophen).
2. *Pyrazolone derivatives*: Metamizol (Dipyrone), Propiphenazone.
3. *Benzoxazocine derivative*: Nefopam.

NSAIDs and prostaglandin (PG) synthesis inhibition

In 1971 Vane and coworkers made the landmark observation that aspirin and some NSAIDs blocked PG generation. This is now considered to be the major mechanism of action of NSAIDs. Prostaglandins, prostacyclin (PG I_2) and thromboxane A_2 (TXA_2) are produced from arachidonic acid by the enzyme cyclooxygenase (*see* p. 182) which exists in a constitutive (COX-1) and an inducible (COX-2) isoforms; the former serves physiological 'house keeping' functions, while the latter, normally present in minute quantities, is induced by cytokines and other signal molecules at the site of inflammation → generation of PGs locally which mediate many of the inflammatory changes. However, COX-2 is constitutively present at some sites in brain, in juxtaglomerular cells and in the foetus; it may serve physiological role at these sites. Most NSAIDs inhibit COX-1 and COX-2 nonselectively, but now some selective COX-2 inhibitors have been produced. Features

of nonselective COX-1/COX-2 inhibitors (traditional NSAIDs) and selective COX-2 inhibitors are compared in Table 14.1

Aspirin inhibits COX irreversibly by acetylating one of its serine residues; return of COX activity depends on synthesis of fresh enzyme.

Beneficial actions due to PG synthesis inhibition

- Analgesia: prevention of pain nerve ending sensitization
- Antipyresis
- Antiinflammatory
- Antithrombotic
- Closure of ductus arteriosus in newborn

Other NSAIDs are competitive and reversible inhibitors of COX; return of activity depends on their dissociation from the enzyme which in turn is governed by the pharmacokinetic characteristics of the compound.

Analgesia PGs induce hyperalgesia (*see* p. 187) by affecting the transducing property of free nerve endings so that stimuli that normally do not elicit pain are able to do so. NSAIDs do not affect the tenderness induced by direct application of PGs, but block the pain sensitizing mechanism induced by bradykinin, TNFα, interleukins (ILs) and other algesic substances primarily by inhibiting COX-2. This constitutes the peripheral component of the analgesic action of NSAIDs. They are, therefore, more effective against inflammation associated pain.

Lately the central component of analgesic action of NSAIDs has also been shown to involve inhibition of PG synthesis in the spinal dorsal horn neurones as well as in brain.

Antipyresis NSAIDs reduce body temperature in fever, but do not cause hypothermia in normothermic individuals. Fever during infection and tissue injury is produced through the generation of pyrogens including, ILs, TNFα, interferons which induce PGE_2 production in hypothalamus—raise its temperature set point. NSAIDs block the action of pyrogens but not that of PGE_2 injected into the hypothalamus. The isoform present at this site appears to be COX-2 (possibly COX-3 also). However, fever can occur through non-PG mediated mechanisms as well.

Shared toxicities due to PG synthesis inhibition

- Gastric mucosal damage
- Bleeding: inhibition of platelet function
- Limitation of renal blood flow : Na^+ and water retention
- Delay/prolongation of labour
- Asthma and anaphylactoid reactions in susceptible individuals

Antiinflammatory The most important mechanism of antiinflammatory action of NSAIDs is considered to be inhibition of COX-2 mediated enhanced PG synthesis at the site of injury. However, there is some evidence that inhibition of the constitutive COX-1 also contributes to suppression of inflammation, especially in the initial stages. The antiinflammatory potency of different compounds roughly corresponds with their potency to inhibit COX. However, nimesulide is a potent antiinflammatory but relatively weak COX inhibitor. PGs are only one of the mediators of inflammation; inhibition of COX does not depress the production of other mediators like LTs, PAF, cytokines, etc. Inflammation is the result of concerted participation of a large number of vasoactive, chemotactic and proliferative factors at different stages, and there are many targets for antiinflammatory action.

Activated endothelial cells express adhesion molecules (ELAM-1, ICAM-1) on their surface and play a key role in directing circulating leucocytes to the site of inflammation (chemotaxis). Similarly, inflammatory cells express *selectins* and *integrins*. Certain NSAIDs may act by additional mechanisms including inhibition of expression/activity of some of these molecules and generation of superoxide/other free radicals. Growth factors like GM-CSF, IL-6 as well as lymphocyte transformation factors and TNFα may also be affected. Stabilization of leucocyte lysosomal membrane and antagonism of certain actions of kinins may be contributing to NSAID action.

Dysmenorrhoea Involvement of PGs in dysmenorrhoea has been clearly demonstrated: level of

TABLE 14.1 Features of nonselective COX inhibitors and selective COX-2 inhibitors

Action	COX-1/COX-2 inhibitors	COX-2 inhibitors
1. Analgesic	+	+
2. Antipyretic	+	+
3. Antiinflammatory	+	+
4. Antiplatelet aggregatory	+	–
5. Gastric mucosal damage	+	–
6. Renal salt/water retention	+	+
7. Delay/prolongation of labour	+	+
8. Ductus arteriosus closure	+	?
9. Aspirin sensitive asthma precipitation	+	–

PGs in menstrual flow, endometrial biopsy and that of $PGF_{2\alpha}$ metabolite in circulation are raised in dysmenorrhoeic women. Intermittent ischaemia of the myometrium is probably responsible for menstrual cramps. NSAIDs lower uterine PG levels—afford excellent relief in 60–70% and partial relief in the remaining. Ancillary symptoms of headache, muscle ache and nausea are also relieved. Excess flow may be normalized.

Antiplatelet aggregatory NSAIDs inhibit synthesis of both proaggregatory (TXA_2) and antiaggregatory (PGI_2) prostanoids, but effect on platelet TXA_2 (COX-1 generated) predominates → therapeutic doses of most NSAIDs inhibit platelet aggregation: bleeding time is prolonged. Aspirin is highly active; acetylates platelet COX irreversibly in the portal circulation before it is deacetylated by first pass metabolism in liver. Small doses are therefore able to exert antithrombotic effect for several days. Risk of surgical and anticoagulant associated bleeding is enhanced.

Ductus arteriosus closure During foetal circulation ductus arteriosus is kept patent by local elaboration of PGE_2 by COX-2. Unknown mechanisms switch off this synthesis at birth and the ductus closes. When this fails to occur, small doses of indomethacin or aspirin bring about closure in majority of cases within a few hours by inhibiting PG production. Administration of NSAIDs in late pregnancy has been found to promote premature closure of ductus in some cases. Risk of post-partum haemorrhage is increased. Prescribing of NSAIDs near term should be avoided.

Parturition Sudden spurt of PG synthesis by uterus occurs just before labour begins. This is believed to trigger labour as well as facilitate its progression. Accordingly, NSAIDs have the potential to delay and retard labour. However, labour can occur in the absence of PGs.

Gastric mucosal damage Gastric pain, mucosal erosion/ulceration and blood loss are produced by all NSAIDs to varying extents: relative gastric toxicity is a major consideration in the choice of NSAIDs. Inhibition of COX-1 mediated synthesis of gastroprotective PGs (PGE_2, PGI_2) is clearly involved, though local action inducing back diffusion of H^+ ions in gastric mucosa also plays a role. Deficiency of PGs reduces mucus and HCO_3^- secretion, tends to enhance acid secretion and may promote mucosal ischaemia. Thus, NSAIDs enhance aggressive factors and contain defensive factors in gastric mucosa—are ulcerogenic. Paracetamol, a very weak inhibitor of COX is practically free of gastric toxicity and selective COX-2 inhibitors are relatively safer. Stable PG analogues (misoprostol) administered concurrently with NSAIDs counteract their gastric toxicity.

Renal effects Conditions leading to hypovolaemia, decreased renal perfusion and Na^+ loss induce renal PG synthesis which brings about intrarenal adjustments by promoting vasodilatation, inhibiting tubular Cl^- reabsorption (Na^+ and water accompany) and opposing ADH action. NSAIDs produce renal effects by at least 3 mechanisms:

- COX-1 dependent impairment of renal blood flow and reduction of g.f.r. → can worsen renal insufficiency.
- Juxtaglomerular COX-2 (probably COX-1 also) dependent Na^+ and water retention.
- Ability to cause papillary necrosis on habitual intake.

Renal effects of NSAIDs are not marked in normal individuals, but become significant in those with CHF, hypovolaemia, hepatic cirrhosis, renal disease and in patients receiving diuretics or antihypertensives. In them Na^+ retention and edema can occur; diuretic and antihypertensive drug effects are blunted.

Involvement of PG synthesis inhibition in analgesic nephropathy is uncertain.

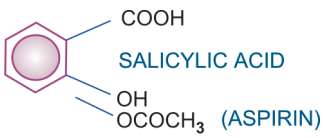
Analgesic nephropathy occurs after years of heavy ingestion of analgesics. Such individuals probably have some personality defect. Regular use of combinations of NSAIDs and chronic/ repeated urinary tract infections increase the risk of analgesic nephropathy. Pathological lesions are papillary necrosis, tubular atrophy followed by renal fibrosis. Urine concentrating ability is lost and the kidneys shrink. Because phenacetin was first implicated, it went into disrepute, though other analgesics are also liable to produce similar effects.

Anaphylactoid reactions Aspirin precipitates asthma, angioneurotic swellings, urticaria or rhinitis in certain susceptible individuals. These subjects react similarly to chemically diverse NSAIDs, ruling out immunological basis for the reaction. Inhibition of COX with consequent diversion of arachidonic acid to LTs and other products of lipoxygenase pathway may be involved, but there is no proof.

SALICYLATES

Aspirin (prototype)

Aspirin is acetylsalicylic acid. It is rapidly converted in the body to salicylic acid which is responsible for most of the actions. Other actions are the result of acetylation of certain macromolecules including COX. It is one of the oldest analgesic-antiinflammatory drugs and is still frequently used.



PHARMACOLOGICAL ACTIONS

1. Analgesic, antipyretic, antiinflammatory actions Aspirin is a weaker analgesic (has lower maximal efficacy) than morphine type drugs: aspirin 600 mg ≃ codeine 60 mg. However, it effectively relieves inflammatory, tissue injury related, connective tissue and integumental pain, but is relatively ineffective in severe visceral and ischaemic pain. The analgesic action is mainly due to obtunding of peripheral pain receptors and prevention of PG-mediated sensitization of nerve endings. A central subcortical action raising threshold to pain perception also contributes, but the morphine-like action on psychic processing or reaction component of the pain is missing. No sedation, subjective effects, tolerance or physical dependence is produced.

Aspirin resets the hypothalamic thermostat and rapidly reduces fever by promoting heat loss (sweating, cutaneous vasodilatation), but does not decrease heat production.

Antiinflammatory action is exerted at high doses (3–6 g/day or 100 mg/kg/ day). Signs of inflammation like pain, tenderness, swelling, vasodilatation and leucocyte infiltration are suppressed. In addition to COX inhibition, quenching of free radicals may contribute to its antiinflammatory action.

2. Metabolic effects These are significant only at antiinflammatory doses. Cellular metabolism is increased, especially in skeletal muscles, due to uncoupling of oxidative phosphorylation → increased heat production. There is increased utilization of glucose → blood sugar may decrease (especially in diabetics) and liver glycogen is depleted. However, hyperglycaemia often occurs at toxic doses: this is due to central sympathetic stimulation → release of Adr and corticosteroids. Chronic use of large doses cause negative N_2 balance by increased conversion of protein to carbohydrate. Plasma free fatty acid and cholesterol levels are reduced.

3. Respiration The effects are dose dependent. At antiinflammatory doses, respiration is stimulated by peripheral (increased CO_2 production) as well as central (increased sensitivity of respiratory centre to CO_2) actions. Hyperventilation is prominent in salicylate poisoning. Further rise in salicylate level causes respiratory depression; death is due to respiratory failure.

4. Acid-base and electrolyte balance Usual analgesic doses (0.3–1.0 g) have practically no effect. Antiinflammatory doses produce significant changes in the acid-base and electrolyte composition of body fluids. Initially, respiratory stimulation predominates and tends to wash out CO_2 despite increased production → respiratory alkalosis, which is compensated by increased renal excretion of HCO_3^- (with accompanying Na^+, K^+ and water). Most adults treated with 4–5 g/day of aspirin stay in a state of *compensated respiratory alkalosis.*

Still higher doses cause respiratory depression with CO_2 retention, while excess CO_2 production continues → *respiratory acidosis*. To this are added dissociated salicylic acid as well as metabolic acids (lactic, pyruvic, acetoacetic) which are produced in excess + metabolically derived sulfuric and phosphoric acid which are retained due to depression of renal function. All these combine to cause *uncompensated metabolic acidosis* since plasma HCO_3^- is already low. Most children manifest this phase during salicylate poisoning; while in adults it is seen in late stages of poisoning only.

Dehydration occurs in poisoning due to increased water loss in urine (to accompany Na^+, K^+ and HCO_3^-) increased sweating and hyperventilation.

5. CVS Aspirin has no direct effect on heart or blood vessels in therapeutic doses. Larger doses increase cardiac output to meet the increased peripheral O_2 demand, and cause direct vasodilatation. Toxic doses depress vasomotor centre: BP may fall. Because of increased cardiac work as well as Na^+ and water retention, CHF may be precipitated in patients with low cardiac reserve.

6. GIT Aspirin and released salicylic acid irritate gastric mucosa → cause epigastric distress, nausea and vomiting. It also stimulates CTZ: vomiting that occurs at higher doses has a central component as well.

Aspirin (pKa 3.5) remains unionized and diffusible in the acid gastric juice, but on entering the mucosal cell (pH 7.1) it ionizes and becomes indiffusible. This 'ion trapping' in the gastric mucosal cell enhances gastric toxicity. Further, aspirin particle coming in contact with gastric mucosa promotes local back diffusion of acid → focal necrosis of mucosal cells and capillaries → acute ulcers, erosive gastritis, congestion and microscopic haemorrhages. The occult blood loss in stools is increased by even a single tablet of aspirin. Blood loss averages 5 ml/day at antiinflammatory doses. Haematemesis occurs occasionally: may be an idiosyncratic reaction.

Soluble aspirin tablets containing calcium carbonate + citric acid and other buffered preparations are less liable to cause gastric irritation, but incidence of ulceration and bleeding is not significantly lowered.

7. Urate excretion Dose-related effect is seen:

< 2 g/day—urate retention and antagonism of all other uricosuric drugs.

2–5 g/day—variable effects, often no change.

> 5 g/day—increased urate excretion.

Aspirin is not suitable for use in chronic gout.

8. Blood Aspirin, even in small doses, irreversibly inhibits TXA_2 synthesis by platelets. Thus, it interferes with platelet aggregation and bleeding time is prolonged to nearly twice the normal value. This effect lasts for about a week (turnover time of platelets).

Long-term intake of large dose decreases synthesis of clotting factors in liver and predisposes to bleeding. This can be prevented by prophylactic vit K therapy.

PHARMACOKINETICS

Aspirin is absorbed from the stomach and small intestines. Its poor water solubility is the limiting factor in absorption: microfining the drug-particles and inclusion of an alkali (solubility is more at higher pH) enhances absorption. However, higher pH also favours ionization, thus decreasing the diffusible form.

Aspirin is rapidly deacetylated in the gut wall, liver, plasma and other tissues to release salicylic acid which is the major circulating

and active form. It is ~80% bound to plasma proteins and has a volume of distribution ~0.17 L/kg. Entry into brain is slow, but aspirin freely crosses placenta. Both aspirin and salicylic acid are conjugated in liver with glycine to form salicyluric acid (major pathway). They are also conjugated with glucuronic acid. Few other minor metabolites are also produced. The metabolites are excreted by glomerular filtration and tubular secretion. Normally, only 1/10th is excreted as free salicylic acid, but this can be increased by alkalinization.

The plasma t½ of aspirin as such is 15–20 min, but taken together with that of released salicylic acid, it is 3–5 hours. However, metabolic processes get saturated over the therapeutic range; t½ of antiinflammatory doses may be 8–12 hours while that during poisoning may be as high as 30 hours. Thus, elimination is dose dependent.

ADVERSE EFFECTS

(a) *Side effects* that occur at analgesic dose (0.3–1.5 g/day) are nausea, vomiting, epigastric distress, increased occult blood loss in stools. The most important adverse effect of aspirin is gastric mucosal damage and peptic ulceration.

(b) *Hypersensitivity and idiosyncrasy* Though infrequent, these can be serious. Reactions include rashes, fixed drug eruption, urticaria, rhinorrhoea, angioedema, asthma and anaphylactoid reaction. Profuse gastric bleeding occurs in rare instances.

(c) *Antiinflammatory doses* (3–5 g/day) produce the syndrome called salicylism—dizziness, tinnitus, vertigo, reversible impairment of hearing and vision, excitement and mental confusion, hyperventilation and electrolyte imbalance. The dose has to be titrated to one which is just below that producing these symptoms; tinnitus is a good guide.

Aspirin therapy in children with rheumatoid arthritis has been found to raise serum transaminases, indicating liver damage. Most cases are asymptomatic but it is potentially dangerous. An association has been noted between salicylate therapy and 'Reye's syndrome', a rare form of hepatic encephalopathy seen in children having viral (varicella, influenza) infection.

In adults also, long-term therapy with high dose aspirin can cause insidious onset hepatic injury. Salt and water retention occurs in a dose related manner.

(d) *Acute salicylate poisoning* It is more common in children. Fatal dose in adults is estimated to be 15–30 g, but is considerably lower in children. Serious toxicity is seen at serum salicylate levels > 50 mg/dl. Manifestations are:

Vomiting, dehydration, electrolyte imbalance, acidotic breathing, hyper/hypoglycaemia, petechial haemorrhages, restlessness, delirium, hallucinations, hyperpyrexia, convulsions, coma and death due to respiratory failure + cardiovascular collapse.

Treatment is symptomatic and supportive. Most important is external cooling and i.v. fluid with Na^+, K^+, HCO_3^- and glucose: according to need determined by repeated monitoring. Gastric lavage to remove unabsorbed drug; alkaline diuresis or haemodialysis to remove absorbed drug is indicated in severe cases. Blood transfusion and vit K should be given if bleeding occurs.

Precautions and contraindications

- Aspirin is contraindicated in patients who are sensitive to it and in peptic ulcer, bleeding tendencies, in children suffering from chicken pox or influenza. Due to risk of Reye's syndrome pediatric formulations of aspirin are prohibited in India and the UK.
- Cautious use in chronic liver disease: cases of hepatic necrosis have been reported.
- It should be avoided in diabetics, in those with low cardiac reserve or frank CHF and in juvenile rheumatoid arthritis.
- Aspirin should be stopped 1 week before elective surgery.
- Given chronically during pregnancy it may be responsible for low birth weight babies. Delayed or prolonged labour, greater

postpartum blood loss and premature closure of ductus arteriosus are possible if aspirin is taken at or near term.
- It should be avoided by breastfeeding mothers.
- Avoid high doses in G-6PD deficient individuals—haemolysis can occur.

Interactions

1. Aspirin displaces warfarin, naproxen, sulfonylureas, phenytoin and methotrexate from binding sites on plasma proteins: toxicity of these drugs may occur. Its antiplatelet action increases the risk of bleeding in patients on oral anticoagulants.
2. Aspirin at analgesic doses inhibits tubular secretion of uric acid and antagonizes uricosuric action of probenecid. Tubular secretion of methotrexate is also interfered.
3. Aspirin blunts diuretic action of furosemide and thiazides and reduces K^+ conserving action of spironolactone. Competition between canrenone (active metabolite of spironolactone) and aspirin for active transport in proximal tubules has been demonstrated.
4. Aspirin reduces protein bound iodine levels by displacement of thyroxine; but hypothyroidism does not occur.

USES

1. *As analgesic* For headache (including mild migraine), backache, myalgia, joint pain, pulled muscle, toothache, neuralgias and dysmenorrhoea; it is effective in low doses (0.3–0.6 g 6–8 hourly). Analgesic effect is maximal at ~ 1000 mg (single dose).

2. *As antipyretic* Aspirin is effective in fever of any origin; dose is same as for analgesia. However, paracetamol, being safer, is generally preferred. Antipyretics are not useful in fever due to heat stroke; only external cooling lowers body temperature.

3. *Acute rheumatic fever* Aspirin is the first drug to be used in all cases; other drugs are added or substituted only when it fails or in severe cases (corticosteroids act faster). In a dose of 4–5 g or 75–100 mg/kg/day (in divided portions producing steady state serum salicylate concentration 15–30 mg/dl) it brings about marked symptomatic relief in 1–3 days. Dose reduction may be started after 4–7 days and maintenance doses (50 mg/kg/day) are continued for 2–3 weeks or till signs of active disease (raised ESR) persist. Withdrawal should be gradual over the next 2 weeks.

Granulomatous lesions, nodules, cardiac complications, valvular defects, chorea and duration of disease are not altered by salicylate therapy.

4. *Rheumatoid arthritis* Aspirin in a dose of 3–5 g/day is effective in most cases; produces relief of pain, swelling and morning stiffness, but progress of the disease process is not affected. Since large doses of aspirin are poorly tolerated for long periods it is rarely used now; other NSAIDs are preferred.

Adverse effects of NSAIDs

Gastrointestinal
Nausea, anorexia, gastric irritation, erosions, peptic ulceration, gastric bleeding/perforation, esophagitis

Renal
Na^+ and water retention, chronic renal failure, nephropathy, papillary necrosis (rare)

CVS
Rise in BP, risk of myocardial infarction (especially with COX-2 inhibitors)

Hepatic
Raised transaminases, hepatic failure (rare)

CNS
Headache, mental confusion, vertigo, behavioural disturbances, seizure precipitation

Haematological
Bleeding, thrombocytopenia, haemolytic anaemia, agranulocytosis

Others
Asthma exacerbation, rhinitis, nasal polyposis, skin rashes, pruritus, angioedema

5. *Osteoarthritis* It affords symptomatic relief only; may be used on 'as and when required' basis, but paracetamol is the first choice analgesic for most cases.

6. *Postmyocardial infarction and poststroke patients* By inhibiting platelet aggregation aspirin lowers the incidence of reinfarction. TXA_2 synthesis in platelets is inhibited at low doses. It has been argued that high doses can reverse the beneficial effects by concurrently inhibiting PGI_2 (antiaggregatory and vasodilatory) synthesis in vessel wall. Large studies have demonstrated that aspirin 60–100 mg/day reduces the incidence of myocardial infarction (MI): it is now routinely prescribed to post-infarct patients. Some authorities recommend it for primary prophylaxis as well, but the risk of bleeding has to be weighed against the possible benefit. 'New onset' or 'sudden worsening' angina is associated with high infarction rate. This can be reduced to half by 100–150 mg aspirin per day for 12 weeks.

Aspirin reduces 'transient ischaemic attacks' and lowers incidence of stroke in such patients. But the risk of stroke in post-MI patients is not reduced.

7. Other less well established uses of aspirin are:
(a) Pregnancy-induced hypertension and pre-eclampsia: imbalance between TXA_2 and PGI_2 is believed to be involved: aspirin 80–100 mg/day benefits many cases by selectively suppressing TXA_2 production.
(b) Patent ductus arteriosus: aspirin can bring about closure and avoid surgery.

Comorbid conditions aggravated by NSAIDs

- Peptic ulcer
- Hypertension
- Congestive heart failure
- Renal insufficiency
- Hemostatic disorders

(c) Familial colonic polyposis: aspirin and other NSAIDs suppress polyp formation and afford symptomatic relief in this rare disorder.
(d) Prevention of colon cancer: incidence of colon cancer among regular aspirin users is much lower. Colonic tumours express large quantities of COX-2. However, the rofecoxib trial (APPROVE) was prematurely terminated and the drug withdrawn due to increased incidence of cardiovascular events. The Adenoma Prevention with Celecoxib (APC) trial has also been terminated due to 2.5 fold increase in risk of major fatal/nonfatal cardiovascular events.
(e) To prevent flushing attending nicotinic acid ingestion, which is due to PGD_2 release in the skin.

ASPIRIN 350 mg tab, COLSPRIN 100, 325 mg tabs, ECOSPRIN 75, 150, 325 mg tabs, DISPRIN 350 mg tab (with cal. carbonate 105 mg + citric acid 35 mg), LOPRIN 75, 162.5 mg tabs.
An injectable preparation has also been made available; BIOSPIRIN: Lysine acetylsalicylate 900 mg + glycine 100 mg/vial for dissolving in 5 ml water and i.v. injection.

Other salicylates (salicylamide, benorylate, diflunisal) are not in use.

PROPIONIC ACID DERIVATIVES

Ibuprofen was the first member of this class to be introduced in 1969 as a better tolerated alternative to aspirin. Many others have followed. All have similar pharmacodynamic properties but differ considerably in potency and to some extent in duration of action (Table 14.2).

Drug interactions with NSAIDs

Pharmacodynamic		Pharmacokinetic	
Diuretics	: ↓ diuresis	Oral anticoagulants Sulfonylureas Phenytoin Valproate	Metabolism inhibited; competition for plasma protein binding
β blocker	: ↓ antihypertensive effect		
ACE inhibitors	: ↓ antihypertensive effect		
Anticoagulants	: ↑ risk of g.i. bleed		
Sulfonylureas	: ↑ risk of hypoglycaemia		
Alcohol	: ↑ risk of g.i. bleed		
Cyclosporine	: ↑ nephrotoxicity	Digoxin Lithium Aminoglycosides Methotrexate	↓ Renal excretion of interacting drug
Corticosteroids	: ↑ risk of g.i. bleed		
Selective serotonin reuptake inhibitors	: ↑ risk of g.i. bleed		

TABLE 14.2 **Dosage and preparations of propionic acid derivatives**

	Drug	*Plasma t½*	*Dosage*	*Preparations*
1.	Ibuprofen	2-4 hr	400–600 mg (5–10 mg/kg) TDS	BRUFEN, EMFLAM, IBUSYNTH 200, 400, 600 mg tab, IBUGESIC also 100 mg/5 ml susp.
2.	Naproxen	12–16 hr	250 mg BD–TDS	NAPROSYN, NAXID, ARTAGEN, XENOBID 250 mg tab., NAPROSYN also 500 mg tab.
3.	Ketoprofen	2–3 hr	50–100 mg BD–TDS	KETOFEN 50, 100 mg tab; OSTOFEN 50 mg cap. RHOFENID 100 mg tab, 200 mg SR tab; 100 mg/2 ml amp.
4.	Flurbiprofen	4–6 hr	50 mg BD–QID	ARFLUR 50, 100 mg tab, 200 mg SR tab, FLUROFEN 100 mg tab.

The analgesic, antipyretic and antiinflammatory efficacy is rated somewhat lower than high dose of aspirin. All members inhibit PG synthesis, naproxen being the most potent; but their *in vitro* potency to inhibit COX does not closely parallel *in vivo* antiinflammatory potency. Inhibition of platelet aggregation is short-lasting with ibuprofen, but longer lasting with naproxen.

Adverse effects Ibuprofen and all its congeners are better tolerated than aspirin. Side effects are milder and their incidence is lower.

Gastric discomfort, nausea and vomiting, though less than aspirin or indomethacin, are still the most common side effects. Gastric erosion and occult blood loss are rare.

CNS side effects include headache, dizziness, blurring of vision, tinnitus and depression.

Rashes, itching and other hypersensitivity phenomena are infrequent. However, these drugs precipitate aspirin-induced asthma.

Fluid retention is less marked.

They are not to be prescribed to pregnant women and should be avoided in peptic ulcer patient.

Pharmacokinetics and interactions All are well absorbed orally, highly bound to plasma proteins (90–99%), but displacement interactions are not clinically significant—dose of oral anticoagulants and oral hypoglycaemics need not be altered. Because they inhibit platelet function, use with anticoagulants should, nevertheless, be avoided. Similar to other NSAIDs, they are likely to decrease diuretic and antihypertensive action of thiazides, furosemide and β blockers.

All propionic acid derivatives enter brain, synovial fluid and cross placenta. They are largely metabolized in liver by hydroxylation and glucuronide conjugation and excreted in urine as well as bile.

Uses

1. Ibuprofen is used as a simple analgesic and antipyretic in the same way as low dose of aspirin. It is particularly effective in dysmenorrhoea in which the action is clearly due to PG synthesis inhibition. It is available as an 'over-the-counter' drug.
2. Ibuprofen and its congeners are widely used in rheumatoid arthritis, osteoarthritis and other musculoskeletal disorders, especially where pain is more prominent than inflammation.
3. They are indicated in soft tissue injuries, fractures, vasectomy, tooth extraction, postpartum and postoperatively: suppress swelling and inflammation.

Ibuprofen It has been rated as the safest traditional NSAID by the spontaneous adverse drug reaction reporting system in U.K. Ibuprofen (400 mg) has been found equally or more efficacious than a combination of aspirin (650 mg) + codeine (60 mg) in relieving dental surgery pain, but is a weaker antiinflammatory; not suitable for acute gout and other similar conditions.

Concurrent treatment with ibuprofen has been found to prevent irreversible COX inhibition by low dose aspirin by reversibly occupying the active serine residue of COX-1 and protecting it from irreversible acetylation by aspirin. Thus, the antiplatelet action of ibuprofen is short

lasting and it antagonizes the antiplatelet and cardioprotective effect of low dose aspirin.

Naproxen The antiinflammatory activity is stronger and it is particularly potent in inhibiting leucocyte migration—may be more valuable in acute gout: dose 750 mg stat followed by 250 mg 8 hourly till attack subsides. It is also recommended for rheumatoid arthritis and ankylosing spondylitis. Because of longer t½ regular use can effectively suppress platelet function. Naproxen carries lower thrombotic risk than diclofenac, etoricoxib, etc. Dose should be reduced in the elderly.

Naproxen is marketed as active single S(–) enantiomer preparation, which poses less renal burden. However, some R(+) enantiomer is formed *in vivo* due to inversion.

Ketoprofen An additional action to stabilize lysosomes and inhibit LOX has been demonstrated with ketoprofen; though antiinflammatory efficacy is similar to ibuprofen, and side effects are more.

Flurbiprofen more effective than ibuprofen, but gastric side effects are also more. It is used as an ocular antiinflammatory as well.
OCUFLUR, FLUR, FLURBIN, 0.03% eyedrops, 1 drop 6 hourly.

Choice among different propionic acid derivatives is difficult; *naproxen* is probably more efficacious and better tolerated in antiinflammatory doses. It is longer acting and has the advantage of twice daily dosing. However, individuals vary in their preference for different members.

FENAMATE (Anthranilic acid derivative)

Mephenamic acid An analgesic, antipyretic and weaker antiinflammatory drug, which inhibits synthesis of PGs as well as antagonises some of their actions. Mephenamic acid exerts peripheral as well as central analgesic action.

Adverse effects Diarrhoea is the most important dose-related side effect. Epigastric distress is complained, but gut bleeding is not significant. Skin rashes, dizzines and other CNS manifestations have occurred. Haemolytic anaemia is a rare but serious complication.

Pharmacokinetics Oral absorption is slow but almost complete. It is highly bound to plasma proteins—displacement interactions can occur; partly metabolized and excreted in urine as well as bile. Plasma t½ is 2–4 hours.

Uses Mephenamic acid is indicated primarily as analgesic in muscle, joint and soft tissue pain where strong antiinflammatory action is not needed. It is quite effective in dysmenorrhoea. It may be useful in some cases of rheumatoid and osteoarthritis but has no distinct advantage.
Dose: 250–500 mg TDS; MEDOL 250, 500 mg cap; MEFTAL 250, 500 mg tab, 100 mg/5 ml susp.
PONSTAN 125, 250, 500 mg tab, 50 mg/ml syrp.

ENOLIC ACID DERIVATIVES (Oxicams)

Piroxicam It is a long-acting potent NSAID with antiinflammatory potency similar to indomethacin and good analgesic-antipyretic action. It is a nonselective, reversible inhibitor of COX; lowers PG concentration in synovial fluid and inhibits platelet aggregation—prolonging bleeding time. In addition, it decreases the production of IgM rheumatoid factor and leucocyte chemotaxis. Thus, it can inhibit inflammation in diverse ways.

Pharmacokinetics It is rapidly and completely absorbed: 99% plasma protein bound; largely metabolized in liver by hydroxylation and glucuronide conjugation; excreted in urine and bile; enterohepatic cycling occurs. Plasma t½ is long—nearly 2 days. Steady-state concentrations are achieved in a week. Single daily administration is sufficient.

Adverse effects The g.i. side effects are more than ibuprofen, but it is better tolerated and less ulcerogenic than indomethacin; causes less faecal blood loss than aspirin. Rashes and pruritus are seen in < 1% patients, but serious skin reactions are possible. Edema and reversible azotaemia have been observed.

Uses Due to slow onset of action piroxicam is suitable for use as long-term antiinflammatory drug in rheumatoid and osteo-arthritis,

ankylosing spondylitis, etc., but is not a first choice drug for any condition because of relatively higher toxicity. It has also been used for acute gout, musculoskeletal injuries and in dentistry.

Dose: 20 mg BD for two days followed by 20 mg OD: DOLONEX, PIROX 10, 20 mg cap, 20 mg dispersible tab, 20 mg/ml inj in 1 and 2 ml amps; PIRICAM 10, 20 mg cap.

Tenoxicam A congener of piroxicam with similar properties and uses.

TOBITIL 20 mg tab; dose 20 mg OD.

ACETIC ACID DERIVATIVES

Ketorolac This arylacetic acid NSAID has potent analgesic but modest antiinflammatory activity. In postoperative pain it has equalled the efficacy of morphine, but does not interact with opioid receptors and is free of opioid side effects. Like other NSAIDs, it inhibits PG synthesis and relieves pain primarily by a peripheral mechanism. In short-lasting pain, it has compared favourably with aspirin.

Ketorolac is rapidly absorbed after oral and i.m. administration. It is highly plasma protein bound and 60% excreted unchanged in urine. Major metabolic pathway is glucuronidation; plasma t½ is 5–7 hours.

Adverse effects Nausea, abdominal pain, dyspepsia, ulceration, loose stools, drowsiness, headache, dizziness, nervousness, pruritus, pain at injection site, rise in serum transaminase and fluid retention have been noted.

Ketorolac has been used concurrently with morphine to keep its dose low. However, it should not be given to patients on anticoagulants.

Use Ketorolac is frequently used in postoperative, dental and acute musculoskeletal pain: 15–30 mg i.m. or i.v. every 4–6 hours (max. 90 mg/day). It may also be used for renal colic, migraine and pain due to bony metastasis.

Orally it is used in a dose of 10–20 mg 6 hourly for short-term management of moderate pain. Ketorolac has been rated superior to aspirin (650 mg), paracetamol (600 mg) and equivalent to ibuprofen (400 mg). Continuous use for more than 5 days is not recommended. It should not be used for preanaesthetic medication or for obstetric analgesia. Topical ketorolac is quite popular for noninfective ocular conditions.

KETOROL, ZOROVON, KETANOV, TOROLAC 10 mg tab, 30 mg in 1 ml amp.

KETLUR, ACULAR 0.5% eye drops; 1–2 drops 2–4 times a day for noninfective ocular inflammatory conditions.

Indomethacin This indole acetic acid derivative is a potent antiinflammatory drug with prompt antipyretic action. Indomethacin relieves only inflammatory or tissue injury related pain. It is a highly potent inhibitor of PG synthesis and suppresses neutrophil motility. In toxic doses it uncouples oxidative phosphorylation (like aspirin).

Pharmacokinetics Indomethacin is well absorbed orally, rectal absorption is slow but dependable. It is 90% bound to plasma proteins, partly metabolized in liver to inactive products and excreted by kidney. Plasma t½ is 2–5 hours.

Adverse effects A high incidence (up to 50%) of gastrointestinal and CNS side effects is produced.

Gastric irritation, nausea, anorexia, gastric bleeding and diarrhoea are prominent.

Frontal headache (very common), dizziness, ataxia, mental confusion, hallucination, depression and psychosis can occur.

Leukopenia, rashes and other hypersensitivity reactions are also reported.

Increased risk of bleeding due to decreased platelet aggregability.

It is contraindicated in machinery operators, drivers, psychiatric patients, epileptics, kidney disease, pregnant women and in children.

Dose: 25–50 mg BD-QID. Those not tolerating the drug orally may be given nightly suppository.

IDICIN, INDOCAP 25 mg cap, 75 mg SR cap, ARTICID 25, 50 mg cap, INDOFLAM 25, 75 mg caps, 1% eye drop. RECTICIN 50 mg suppository.

Uses Because of prominent adverse effects, indomethacin is used as a reserve drug in conditions requiring potent antiinflammatory action like ankylosing spondylitis, acute exacerbations of destructive arthropathies, psoriatic

arthritis and acute gout or rheumatoid arthritis that are not responding to better tolerated NSAIDs.

Malignancy associated fever refractory to other antipyretics may respond to indomethacin. It has been the most common drug used for medical closure of patent ductus arteriosus: three 12 hourly i.v. injections of 0.1–0.2 mg/kg achieve closure in majority of cases.

Bartter's syndrome responds dramatically, as it does to other PG synthesis inhibitors.

Nabumetone It is a prodrug—generates an active metabolite (6-MNA) which inhibits both COX-1 and COX-2. It possesses analgesic, antipyretic and antiinflammatory activities; effective in the treatment of rheumatoid and osteo-arthritis as well as in soft tissue injury. Nabumetone has caused a lower incidence of gastric erosions, ulcers and bleeding, probably because the active COX inhibitor is produced in the tissues after absorption. However, abdominal cramps and diarrhoea can occur, and there is no data on its relative side effect prevalence compared to other NSAIDs. The plasma t½ is 24 hours.

NABUFLAM 500 mg tab; 1 tab OD.

PYRAZOLONES

Antipyrine (phenazone) and amidopyrine (aminopyrine) were introduced in 1884 as antipyretic and analgesic. Their use was associated with high incidence of agranulocytosis: are banned globally. *Phenylbutazone* was introduced in 1949 and soon its active metabolite *oxyphenbutazone* was also marketed. These two are potent antiinflammatory drugs, inhibit COX, but have slow onset, weak analgesic and antipyretic action. Their gastric toxicity is high; edema due to Na^+ and water retention is frequent and CNS side effects, hypersensitivity reactions, hypothyroidism are reported. They have gone out of use due to residual risk of bone marrow depression and other toxicity. Two other pyrazolones available in India—*metamizol* and *propiphenazone* are primarily used as analgesic and antipyretic.

Metamizol (Dipyrone) In contrast to phenylbutazone, this derivative of amidopyrine is a potent and promptly acting analgesic and antipyretic but poor antiinflammatory and not uricosuric. It can be given orally, i.m. as well as i.v, but gastric irritation, pain at injection site occurs. Occasionally, i.v. injection produces precipitous fall in BP.

Few cases of agranulocytosis were reported and metamizol is banned in the USA and some European countries. However, it has been extensively used in India and other European countries. Adverse reaction data collected over four decades shows that risk of serious toxicity with this drug is lower than with aspirin or many other NSAIDs. However, its fixed dose combination with antispasmodics is banned in India.

Dose: 0.5–1.5 g oral/i.m./i.v.; ANALGIN 0.5 g tab; NOVALGIN, BARALGAN 0.5 g tab, 0.5 g/ml in 2 ml and 5 ml amps; ULTRAGIN 0.5 g/ml inj in 2 ml amp and 30 ml vial.

Propiphenazone Another pyrazolone, similar in properties to metamizol; claimed to be better tolerated. Agranulocytosis has not been reported.

Dose: 300–600 mg TDS; marketed only in combination in several 'over-the-counter', preparations—in SARIDON, ANAFEBRIN: propiphenazone 150 mg + paracetamol 250 mg tab.

DART: propiphenazone 150 mg + paracetamol 300 mg + caffeine 50 mg tab.

PREFERENTIAL COX-2 INHIBITORS

Nimesulide This NSAID is a relatively weak inhibitor of PG synthesis and moderately COX-2 selective. Antiinflammatory action may be exerted by other mechanisms as well, e.g. reduced generation of superoxide by neutrophils, inhibition of PAF synthesis and TNFa release, free radical scavanging, inhibition of metalloproteinase activity in cartilage. The analgesic, antipyretic and antiinflammatory activity of nimesulide has been rated comparable to other NSAIDs. It has been used primarily for short-lasting painful inflammatory conditions like sports injuries, sinusitis and other ear-nose-throat disorders, dental surgery, bursitis, low backache, dysmenorrhoea, postoperative pain, osteoarthritis and for fever.

Nimesulide is almost completely absorbed orally, 99% plasma protein bound, extensively metabolized and excreted mainly in urine with a t½ of 2–5 hours.

Adverse effects of nimesulide are gastrointestinal (epigastralgia, heart burn, nausea, loose motions), dermatological (rash, pruritus) and

central (somnolence, dizziness). Gastric tolerability of nimesulide is better, though ulcer complications are as prevalent as with other NSAIDs. Instances of fulminant hepatic failure have been associated with nimesulide and it has been withdrawn in Spain, Ireland, Singapore and Turkey; use in children is banned in Portugal, Israel and now in India as well. A Finish committee for proprietary medicinal products has concluded that hepatic reactions to nimesulide are similar to other NSAIDs. Considering that it has not been marketed in many countries like the UK, USA, Australia, Canada, the overall safety of this drug, especially in children, has been questioned. However, most asthmatics and those who develop bronchospasm or intolerance to aspirin and other NSAIDs do not cross react with nimesulide. Its specific usefulness appears to be only in such patients.
Dose: 100 mg BD; NIMULID, NIMEGESIC, NIMODOL 100 mg tab, 50 mg/5 ml susp.

Diclofenac sodium An analgesic-antipyretic-antiinflammatory drug, similar in efficacy to naproxen. It inhibits PG synthesis and is somewhat COX-2 selective. The antiplatelet action is not appreciable due to sparing of COX-1. It also does not block the cordioprotective effect of low dose aspirin. Neutrophil chemotaxis and superoxide production at the inflammatory site are reduced.

It is well absorbed orally, 99% protein bound, metabolized and excreted both in urine and bile. The plasma t½ is ~2 hours. However, it has good tissue penetrability and concentration in synovial fluid is maintained for 3 times longer period than in plasma, exerting extended therapeutic action in joints.

Adverse effects of diclofenac are generally mild: epigastric pain, nausea, headache, dizziness, rashes. Gastric ulceration and bleeding are less common. Some comparative trials have found its gastric toxicity to be similar to celecoxib and etoricoxib. Like many NSAIDs, diclofenac can increase the risk of heart attack and stroke. Reversible elevation of serum amino-transferases has been reported more commonly; kidney damage is rare.

Diclofenac is among the most extensively used NSAID; employed in rheumatoid and osteoarthritis, bursitis, ankylosing spondylitis, toothache, dysmenorrhoea, renal colic, post-traumatic and postoperative inflammatory conditions—affords quick relief of pain and wound edema.
Dose: 50 mg TDS, then BD oral, 75 mg deep i.m. VOVERAN, DICLONAC, MOVONAC 50 mg enteric coated tab, 100 mg S.R. tab, 25 mg/ml in 3 ml amp. for i.m. inj. DICLOMAX 25, 50 mg tab, 75 mg/3 ml inj.
Diclofenac potassium: VOLTAFLAM 25, 50 mg tab, ULTRA-K 50 mg tab; VOVERAN 1% topical gel.
DICLONAC, VOVERAN OPHTHA 0.1% eye drops.

Aceclofenac A moderately COX-2 selective congener of diclofenac having similar properties. Enhancement of glycosaminoglycan synthesis may confer chondroprotective property to aceclofenac.
Dose: 100 mg BD; ACECLO, DOLOKIND 100 mg tab, 200 mg SR tab.

Meloxicam This newer congener of piroxicam has a COX-2/COX-1 selectivity ratio of about 10. Since measurable inhibition of platelet TXA_2 production (a COX-1 function) occurs at therapeutic doses of meloxicam, it has been labelled 'preferential COX-2 inhibitor'. Efficacy of meloxicam in osteo- and rheumatoid arthritis is comparable to piroxicam. Plasma t½ is 15–20 hours permiting single daily dose. In short-term studies, gastric changes with the lower dose (7.5 mg/day) were found to be similar to placebo, but at the higher dose (15 mg/day) they were intermediate between placebo and piroxicam. Gastric side effects of meloxicam are milder, but ulcer complications (bleeding, perforation) have been reported on long-term use. There is no convincing evidence that meloxicam is safer than other NSAIDs.
Dose: 7.5–15 mg OD; MELFLAM, MEL-OD, MUVIK, M-CAM 7.5 mg, 15 mg tabs.

Etodolac This newer indole-acetic acid NSAID is moderately COX-2 selective with properties similar to diclofenac. At lower doses, gastric tolerance is better than older NSAIDs. It is metabolized by hydroxylation and glucuronide conjugation, and excreted in urine with a t½ of 7 hours. Postoperative analgesia with etodolac lasts for 6–8 hours. Side effects are abdominal

pain, rashes and dizziness. It is approved for use in osteo- and rheumatoid arthritis as well as in acute musculoskeletal pain.

Dose: 200–400 mg BD–TDS; ETOVA 200, 300, 400 mg tabs.

SELECTIVE COX-2 INHIBITORS (Coxibs)

Because of the theoretical advantage of inhibiting COX-2 without affecting COX-1 function, some highly selective COX-2 inhibitors have been introduced over the past 2 decades. They cause less gastric mucosal damage; occurrence of peptic ulcer and ulcer bleeds is clearly lower than with traditional NSAIDs. They do not depress TXA_2 production by platelets (COX-1 dependent); do not inhibit platelet aggregation or prolong bleeding time, but reduce PGI_2 production by vascular endothelium.

Currently, 3 selective COX-2 inhibitors (also called coxibs) *Celecoxib*, *Etoricoxib* and *Parecoxib* are available in India. *Rofecoxib* and *Valdecoxib* were withdrawn within few years of marketing for increasing cardiovascular (CV) risk. *Lumiracoxib* marketed only in Europe has been suspended due to hepatotoxicity.

It has been concluded that selective COX-2 inhibitors should be used only in patients at high risk of peptic ulcer, perforation or bleeds. If selected, they should be administered in the lowest dose for the shortest period of time. Moreover, they should be avoided in patients with history of ischaemic heart disease/hypertension/cardiac failure/cerebrovascular disease, who are predisposed to CV events. Combination of low-dose aspirin with COX-2 inhibitors for reducing cardiovascular risk increases gastroduodenal injury, and is not advised.

Concerns, other than cardiovascular, have also been expressed about selective COX-2 inhibitors.

Selective COX-2 inhibitors and cardiovascular risk

COX-2 inhibitors reduce endothelial PGI_2 production without affecting platelet TXA_2 synthesis. This appears to exert prothrombotic influence and enhance CV risk.

- VIGOR (VIOXX gastrointestinal outcomes research) study in over 8000 patients found 4-fold higher incidence of myocardial infarction (MI) in rofecoxib (VIOXX) recipients compared to those on naproxen.
- APPROVE (adenomatous polyp prevention on VIOXX) a placebo controlled trial among subjects with history of colorectal adenomas was stopped prematurely at 3 years because it confirmed higher risk of heart attack and stroke: rofecoxib was withdrawn globally in 2004.
- A metaanalysis of 18 trials with rofecoxib for musculoskeletal disorders has also inferred that it increases incidence of MI.
- Valdecoxib increased occurrence of MI in patients undergoing coronary bypass surgery. There were reports of severe skin reactions as well. It was withdrawn in 2005.
- Though CLASS (celecoxib long-term safety study) did not find any increase in CV events, the APC (adenoma prevention with celecoxib) trial has been terminated prematurely due to 2.5 fold higher risk of the same.
- There is no clear evidence as yet that etoricoxib also increases CV risk.
- A joint committee in USA (2005) has concluded that enough evidence to withdraw all selective COX-2 inhibitors is lacking, but that their labelling should include a warning of CV risk.

Other concerns with selective COX-2 inhibitors

- COX-1 generated PGs may also play a role in inflammation: COX-2 inhibitors may not have as broad range of efficacy as traditional NSAIDs.
- Ulcer injury and *H. pylori* induce COX-2 in gastric mucosa, which may contribute to gastroprotective PG synthesis; COX-2 inhibition may delay ulcer healing. Moreover, part of gastric mucosal COX-2 activity may be constitutive.
- Juxtaglomerular COX-2 is constitutive; its inhibition can cause salt and water retention; pedal edema, precipitation of CHF and rise in BP can occur with all coxibs.

Celecoxib The COX-2 selectivity of celecoxib is modest and similar to that of diclofenac. It exerts antiinflammatory, analgesic and antipyretic actions with low ulcerogenic potential. Comparative trials in rheumatoid arthritis have found it to be as effective as naproxen or diclofenac, without affecting COX-1 activity in gastroduodenal mucosa. Platelet aggregation in response to collagen exposure remained intact in celecoxib recipients and serum TXB_2 levels were not reduced. Though tolerability of celecoxib is better than traditional NSAIDs, still abdominal pain, dyspepsia and mild diarrhoea are the common side effects. Rashes, edema and a small rise in BP have also been noted.

Celecoxib is slowly absorbed, 97% plasma protein bound and metabolized primarily by CYP2C9 with a t½ of ~10 hours. It is approved for use in osteo- and rheumatoid arthritis in a dose of 100–200 mg BD.

CELACT, REVIBRA, COLCIBRA 100, 200 mg caps.

Etoricoxib This newer COX-2 inhibitor has the highest COX-2 selectivity. It is suitable for once-a-day treatment of osteo/rheumatoid/acute gouty arthritis, ankylosing spondylitis, dysmenorrhoea, acute dental surgery pain and similar conditions, without affecting platelet function or damaging gastric mucosa. The t½ is ~ 24 hours. The rate of thrombotic cardiovascular events with etoricoxib use has been found similar to that with diclofenac. However, it should be considered as a treatment option only as per conditions stated above for all COX-2 inhibitors (*see* p. 205). Side effects are dyspepsia, abdominal pain, pedal edema, rise in BP, dry mouth, aphthous ulcers, taste disturbance and paresthesias.

Dose: 60–120 mg OD; ETOSHINE, TOROCOXIA, ETOXIB, NUCOXIA 60, 90, 120 mg tabs.

Parecoxib It is a prodrug of valdecoxib suitable for injection, and to be used in postoperative or similar short-term pain, with efficacy similar to ketorolac. It shares the same risk of serious cutaneous reactions as valdecoxib. Caution is needed in its use; it should be stopped at the first appearance of a rash.

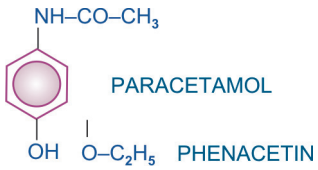
Dose: 40 mg oral/i.m./i.v., repeated after 6–12 hours.

REVALDO, VALTO-P 40 mg/vial inj, PAROXIB 40 mg tab.

PARA-AMINO PHENOL DERIVATIVES

Phenacetin introduced in 1887 was extensively used as analgesic-antipyretic, but is now banned because it was implicated in analgesic abuse nephropathy.

Paracetamol (*acetaminophen*) the deethylated active metabolite of phenacetin, was also introduced in the last century but has come into common use only since 1950.



Actions The central analgesic action of paracetamol is like aspirin, i.e. it raises pain threshold, but has weak peripheral antiinflammatory component. Analgesic action of aspirin and paracetamol is additive. Paracetamol is a good and promptly acting antipyretic.

Paracetamol has negligible antiinflammatory action. It is a poor inhibitor of PG synthesis in peripheral tissues, but more active on COX in the brain. One explanation offered for the discrepancy between its analgesic-antipyretic and antiinflammatory actions is its inability to inhibit COX in the presence of peroxides which are generated at sites of inflammation, but are not present in the brain. The ability of paracetamol to inhibit COX-3 (an isoenzyme so far located in dog brain) could also account for its analgesic-antipyretic action.

In contrast to aspirin, paracetamol does not stimulate respiration or affect acid-base balance; does not increase cellular metabolism. It has no effect on CVS. Gastric irritation is insignificant—mucosal erosion and bleeding occur rarely only in overdose. It does not affect platelet function or clotting factors and is not uricosuric.

Pharmacokinetics Paracetamol is well absorbed orally, only about 1/4th is protein bound in plasma and it is uniformly distributed in the body. Metabolism occurs mainly by conjugation with glucuronic acid and sulfate: conjugates are excreted rapidly in urine. Plasma t½ is 2–3 hours. Effects after an oral dose last for 3–5 hours.

Adverse effects In isolated antipyretic doses paracetamol is safe and well tolerated. Nausea and rashes occur occasionally, leukopenia is rare.

Acute paracetamol poisoning It occurs especially in small children who have low hepatic glucuronide conjugating ability. If a large dose (> 150 mg/kg or > 10 g in an adult) is taken, serious toxicity can occur. Fatality is common with > 250 mg/kg.

Early manifestations are just nausea, vomiting, abdominal pain and liver tenderness with no impairment of consciousness. After 12–18 hours centrilobular hepatic necrosis occurs which may be accompanied by renal tubular necrosis and hypoglycaemia that may progress to coma. Jaundice starts after 2 days. Further course depends on the dose taken. Fulminating hepatic failure and death are likely if the plasma levels are above the line joining 200 µg/ml at 4 hours and 30 µg/ml at 15 hours. If the levels are lower —recovery with supportive treatment is the rule.

Mechanism of toxicity N-acetyl-p-benzoquinoneimine (NAPQI) is a highly reactive arylating minor metabolite of paracetamol which is detoxified by conjugation with glutathione. When a very large dose of paracetamol is taken, glucuronidation capacity is saturated, more of the minor metabolite is formed—hepatic glutathione is depleted and this metabolite binds covalently to proteins in liver cells (and renal tubules) causing necrosis. Toxicity thus shows a threshold effect manifesting only when glutathione is depleted to a critical point.

In chronic alcoholics even 5–6 g taken in one day can result in hepatotoxicity because alcoholism induces CYP2E1 that metabolises paracetamol to NAPQI.

Paracetamol is not recommended in premature infants (< 2 kg) for fear of hepatotoxicity.

Note: Exercising abundant caution, because paracetamol is an over-the-counter drug, the US-FDA (2009) has recommended to reduce the amount of this drug in any single dosage form (tab./cap.) to 650 mg (in place of 1000 mg earlier limit), and the total daily dose for an adult to 2600 mg (in place of 4000 mg earlier). The Drugs Controller General of India (DCGI) has rcently (2011) issued guidelines to limit the amount of paracetamol per dosage form (single tab./cap.) to 325 mg.

Treatment If the patient is brought early, vomiting should be induced or gastric lavage done. Activated charcoal is given orally or through the tube to prevent further absorption. Other supportive measures, as needed, should be taken. *Specific:* N-acetylcysteine (MUCOMIX, ANTIFEN 200 mg/ml inj in 2, 5 ml amps) 150 mg/kg should be infused i.v. over 15 min, followed by the same dose i.v. over the next 20 hours. Alternatively, 75 mg/kg may be given orally every 4–6 hours for 2–3 days. It replenishes the glutathione stores of liver and prevents binding of the toxic metabolite to other cellular constituents.

Ingestion-treatment interval is critical; earlier the better. It is practically ineffective if started 16 hours or more after paracetamol ingestion.

Uses Paracetamol is one of the most commonly used 'over-the-counter' analgesic for headache, mild migraine, musculoskeletal pain, dysmenorrhoea, etc. but is relatively ineffective when inflammation is prominent as in rheumatoid arthritis. Paracetamol is recommended as first choice analgesic for osteoarthritis by many professional bodies. It is one of the best drugs to be used as antipyretic, especially in children (no risk of Reye's syndrome).

Dose to dose it is equally efficacious as aspirin for noninflammatory conditions. It is much safer than aspirin in terms of gastric irritation, ulceration and bleeding (can be given to ulcer patients), does not prolong bleeding time. Hypersensitivity reactions are rare; no metabolic effects or acid-base disturbances; can be used in all age groups (infants to elderly), pregnant/lactating women, in presence of other disease states and in patients in whom aspirin is contraindicated. It does not have significant drug interactions. Thus, it may be preferred over aspirin for most minor conditions.

Dose: 325–650 mg (children 10–15 mg/kg) 3–5 times a day.

CROCIN 0.5, 1.0 g tabs; METACIN, PARACIN 500 mg tab, 125 mg/5 ml syrup, 150 mg/ml paed. drops, ULTRAGIN, PYRIGESIC, CALPOL 500 mg tab, 125 mg/5 ml syrup, NEOMOL, FEVASTIN, FEBRINIL 300 mg/2 ml inj., CROCIN PAIN RELIEF: 650 mg + Caffeine 50 mg tab.
JUNIMOL-RDS 80, 170, 250 mg suppository (for children), PARACETAMOL RECTAL SUPPOSITORY 80, 170 mg.

The DCGI has allowed to manufacturers a period of 3 years to limit the total amount of paracetamol per tab./cap. (single drug or combined formulation) to 325 mg.

BENZOXAZOCINE DERIVATIVE

Nefopam It is a nonopioid analgesic which does not inhibit PG synthesis but relieves traumatic, postoperative and short-lasting musculoskeletal pain. It may be used if pain is persistent and is not adequately relieved by other analgesics.

Nefopam produces anticholinergic (dry mouth, urinary retention, blurred vision) and sympathomimetic (tachycardia, nervousness) side effects, and nausea is often dose limiting. It is contraindicated in epileptics.

Dose: 30–60 mg TDS oral, 20 mg i.m. 6 hourly.

NEFOMAX 30 mg tab, 20 mg in 1 ml amp.

Topical NSAIDs

Many NSAIDs have been marketed in topical formulations (mostly as gels) for application over painful muscles or joints. These preparations are being used for osteoarthritis, sprains, sports injuries, tenosinovitis, backache, spondylitis and other forms of soft tissue rheumatism. It is presumed that the drug would penetrate to the subjacent tissues attaining high concentrations in the affected muscles/joints, while maintaining low blood levels. Consequently the g.i. and other systemic adverse effects would be minimised and first pass hepatic metabolism would also be avoided.

While there is no doubt about their safety, doubt has been raised about their actual efficacy over and above a strong placebo effect of local application, massaging and that due to presence of counter irritants like menthol, methyl salicylate, etc. in most of them. Often they are used in addition to oral NSAID medication; and guidelines of several professional bodies recommend their use in mild-to-moderate osteoarthritis of knee and hand as initial or adjunctive therapy.

Measurement of drug concentration attained in tissues underlying the site of application, as well as concurrent blood levels has shown that systemic absorption from topical NSAID preparations is slow taking ~10 times longer time to attain peak concentration compared to oral dosing. Highest blood levels remain below 15% of the same dose given orally. This is consistent with their lack of systemic toxicity. Local concentrations are high upto a depth of 4–6 mm, i.e. in dermis, but at 25 mm depth in muscles, the concentration is low and nearly the same as in blood. Marked variation has been noted in the concentration attained in muscles and joints depending on the type of formulation, depth and distance from site of application as well as among different individuals. Reports on the clinical efficacy of topical NSAIDs are also variable. Better responses have generally been obtained in short lasting musculoskeletal pain. Clinical trials in osteoarthritis of knee have generally rated topical formulations of NSAIDs, notably those of diclofenac and ketoprofen to be superior to placebo. Though overall efficacy of topical NSAIDs in musculoskeletal pain is low, it appears to be clinically valuable.

Preparations

Diclofenac 1% gel	:	VOLINI GEL, RELAXYL GEL, DICLONAC GEL
Ibuprofen 10% gel	:	RIBUFEN GEL
Naproxen 10% gel	:	NAPROSYN GEL
Ketoprofen 2.5% gel	:	RHOFENID GEL
Flurbiprofen 5% gel	:	FROBEN GEL
Nimesulide 1% gel	:	NIMULID TRANS GEL, ZOLANDIN GEL, NIMEGESIC-T-GEL
Piroxicam 0.5% gel	:	DOLONEX GEL, MOVON GEL, PIROX GEL, MINICAM GEL

Choice of nonsteroidal antiinflammatory drug

Efficacy differences among different NSAIDs are minor, but they have their own spectrum of adverse effects. They differ quantitatively among themselves in producing different side effects and there are large inter-individual differences. At present NSAIDs are a bewildering array of strongly promoted drugs. No single drug is superior to all others for every patient. Choice of drug is inescapably empirical.

The cause and nature of pain (mild, moderate or severe; acute or chronic; ratio of pain: inflammation) along with consideration of risk factors in the given patient (age, concurrent disease and drug therapy, history of allergy) govern selection of the analgesic. Also to be considered are the past experience of the patient, acceptability and individual preference. Patients differ in their analgesic response to different NSAIDs. If one NSAID is unsatisfactory in a patient, it does not mean that other NSAIDs will also be unsatisfactory. Some subjects 'feel better' on a particular drug, but not on a closely related one. It is in this

context that availability of such a wide range of NSAIDs may be welcome. Some guidelines are:

1. Mild-to-moderate pain with little inflammation: paracetamol or low-dose ibuprofen.
2. Postoperative or similar acute but short-lasting pain: ketorolac, a propionic acid derivative, diclofenac or nimesulide.
3. Acute musculoskeletal, osteoarthritic, injury associated pain: paracetamol, a propionic acid derivative or diclofenac.
4. Exacerbation of rheumatoid arthritis, ankylosing spondylitis, acute gout, acute rheumatic fever: naproxen, piroxicam, indomethacin, high dose aspirin.
5. Gastric intolerance to traditional NSAIDs or predisposed patients: a selective COX-2 inhibitor or paracetamol. Arthritis patients who are dependent on NSAIDs and have developed peptic ulcer must receive concurrent proton pump inhibitor as gastroprotective.
6. Patients with history of asthma or anaphylactoid reaction to aspirin/other NSAIDs: nimesulide, COX-2 inhibitor.
7. Patients with hypertension or other risk factor for heart attack/stroke: avoid selective COX-2 inhibitor; a propionic acid derivative or aspirin may be used at the lowest dose for the shortest period.
8. Paediatric patients: only paracetamol, aspirin, ibuprofen and naproxen have been adequately evaluated in children — should be preferred in them. Due to risk of Reye's syndrome, aspirin should be avoided.
9. Elderly patients: use lower dose of the chosen NSAID.
10. Fast acting drug formulation is suitable for fever, headache and other short lasting pain, while longer acting drugs/sustained release formulations are appropriate for chronic arthritic pain.
11. Pregnancy: paracetamol is the safest; low-dose aspirin is probably the second best.
12. Hypertensive, diabetic, ischaemic heart disease, epileptic and other patients receiving long-term regular medication: possibility of drug interaction with NSAIDs should be considered.

Analgesic combinations

Combination of aspirin and paracetamol is additive (not supra-additive) and a ceiling analgesic effect is obtained when the total amount of aspirin + paracetamol is ~ 1000 mg. The same is true of combinations of paracetamol with other NSAIDs like ibuprofen, diclofenac, etc. There is no convincing evidence that such combinations are superior to single agents, either in efficacy or in safety. If at all used, such combinations should be limited to short periods.

Combination of codeine (an opioid analgesic) with aspirin or paracetamol is also additive, but in this case combination provides additional analgesia beyond the ceiling effect of aspirin/paracetamol. However, this is true only when each is given in full dose which will produce opioid side effects as well. The mechanisms of pain relief by these two classes of drugs are different. Such combination should be considered only for pain refractory to single agent.

To obviate inadvertent misuse and chance of producing dependence, the fixed dose combinations of analgesics with hypnotics/sedatives/anxiolytics is banned in India.

☞ PROBLEM DIRECTED STUDY

14.1 A 65-year-old lady presented with pain in both knees, more on the left side. The pain is worsened by walking or standing for some time. X-ray of knee shows narrowing of joint space, mild effusion and osteophytic projections. A diagnosis of osteoarthritis of knee is made. She gave history of suffering a heart attack one year back which was treated by angioplasty and a stent was placed. She regularly takes aspirin 75 mg daily for prophylaxis of further myocardial infarction.

(a) Which analgesic/NSAID will be suitable for relieving her knee pain?

(b) Which analgesic/NSAIDs should not be prescribed for her?

(c) Whether any locally applied medication can be helpful in relieving her knee pain?

(see Appendix-1 for solution)

Chapter 15 Antirheumatoid and Antigout Drugs

ANTIRHEUMATOID DRUGS

These are drugs which (except corticosteroids), can suppress the rheumatoid process, bring about a remission and retard disease progression, but do not have nonspecific antiinflammatory or analgesic action. They are used in rheumatoid arthritis (RA) in addition to NSAIDs and are also referred to as *disease modifying antirheumatic drugs* (DMARDs) or *slow acting antirheumatic drugs* (SAARDs). The onset of benefit with DMARDs takes a few months of regular treatment and relapses occur a few months after cessation of therapy. Recently, some biological agents (antibodies and other proteins) have been added for resistant cases.

Rheumatoid arthritis (RA) is an autoimmune disease in which there is joint inflammation, synovial proliferation and destruction of articular cartilage. Immune complexes composed of IgM activate complement and release cytokines (mainly TNFα and IL-1) which are chemotactic for neutrophils. These inflammatory cells secrete lysosomal enzymes which damage cartilage and erode bone, while PGs produced in the process cause vasodilatation and pain. RA is a chronic progressive, crippling disorder with a waxing and waning course. NSAIDs are the first line drugs and afford symptomatic relief in pain, swelling, morning stiffness, immobility, but do not arrest the disease process.

The goals of drug therapy in RA are:

- Ameliorate pain, swelling and joint stiffness
- Prevent articular cartilage damage and bony erosions
- Prevent deformity and preserve joint function.

Though mild/early cases are still mostly treated with NSAIDs only, the current recommendation is to add DMARDs as soon as the diagnosis of RA is confirmed. However, use of DMARDs in early/mild RA should be weighed against their potential adverse effects, which may be serious. More than one DMARD may be used concurrently; advanced cases may require 2 or 3 drugs together, because all DMARDs tend to lose effectiveness with time.

CLASSIFICATION

I. *Disease modifying antirheumatic drugs (DMARDs)*

A. *Nonbiological drugs*

1. *Immunosuppressants:* Methotrexate, Azathioprine, Cyclosporine
2. Sulfasalazine
3. Chloroquine or Hydroxychloroquine
4. Leflunomide

B. *Biological agents*

1. *TNFα inhibitors:* Etanercept, Infliximab, Adalimumab
2. *IL-1 antagonist:* Anakinra

II. *Adjuvant drugs*

Corticosteroids: Prednisolone and others

(Gold and penicillamine are obsolete DMARDs.)

Nonbiological drugs

1. Immunosuppressants (*see* Ch. 63)

Methotrexate (Mtx) This dihydrofolate reductase inhibitor has prominent immunosuppressant and antiinflammatory property. Beneficial effects in RA are probably related to inhibition of cytokine production, chemotaxis and cell-mediated immune reaction. Induction of oral low-dose (7.5–15 mg) weekly Mtx regimen has improved acceptability of this drug in RA. Onset of symptom relief is relatively rapid (4–6 weeks), therefore preferred

for initial treatment. Mtx is now the DMARD of first choice and the standard treatment for most patients, including cases of juvenile RA. Response is more predictable and sustained over long-term. Combination regimens of 2 or 3 DMARDs include Mtx.

Oral bioavailability of Mtx is variable and may be affected by food. Its excretion is hindered in renal disease: not recommended for such patients. Probenecid and aspirin increase Mtx levels and toxicity. Trimethoprim can add to inhibition of dihydrofolate reductase and depress bone marrow. Oral ulceration and g.i. upset are the major side effects of low dose Mtx regimen. With prolonged therapy, dose dependent progressive liver damage leading to cirrhosis occurs in some patients (this is not seen with short courses used in cancer). Incidence of chest infection is increased. Mtx is contraindicated in pregnancy, breast-feeding, liver disease, active infection, leucopenia and peptic ulcer.

NEOTREXATE, BIOTREXATE 2.5 mg tab.

Azathioprine This purine synthase inhibitor acts after getting converted to 6-mercaptopurine by the enzyme thiopurine methyl transferase (TPMT). It is a potent suppressant of cell-mediated immunity; appears to selectively affect differentiation and function of T-cells and natural killer cells. It also suppresses inflammation. However, remission is induced in smaller percentage of RA patients and it is less commonly used. Given along with corticosteroids, it has a steroid sparing effect, for which it is primarily used now, especially in cases with systemic manifestations. It is not combined with Mtx.

Dose: 50–150 mg/day; IMURAN 50 mg tab.

Other immunosuppressants like cyclosporine, chlorambucil, cyclophosphamide are rarely used in RA; are reserved for cases not responding to other DMARDs.

2. Sulfasalazine (*see* Ch. 48)

It is a compound of sulfapyridine and 5-amino salicylic acid (5-ASA); exerts antiinflammatory activity in the bowel and is useful in ulcerative colitis. In addition, it suppresses the disease in significant number of RA patients. The mechanism of action is not known. Sulfapyridine split off in the colon by bacterial action and absorbed systemically appears to be the active moiety (contrast ulcerative colitis, in which 5-ASA acting locally in the colon is the active component). Generation of superoxide radicals and cytokine elaboration by inflammatory cells may be suppressed. Efficacy of sulfasalazine in RA is modest and side effects may be unpleasant; neutropenia/thrombocytopenia occurs in about 10% patients and hepatitis is possible. It is used as a second line drug for milder cases or is combined wih Mtx.

Dose: 1–3 g/day in 2–3 divided doses.

SALAZOPYRIN, SAZO-EN 0.5 g tab.

3. Chloroquine and hydroxychloroquine (*see* Ch. 59)

These are antimalarial drugs found to induce remission in upto 50% patients of RA, but take 3–6 months. Their advantage is relatively low toxicity, but efficacy is also low; bony erosions are not prevented. Their mechanism of action is not known, however, they have been found to reduce monocyte IL–I, consequently inhibiting B lymphocytes. Antigen processing may be interfered with. Lysosomal stabilization and free radical scavenging are the other proposed mechanisms.

For RA, these drugs have to be given for long periods: accumulate in tissues (especially melanin containing tissue) and produce toxicity, most disturbing of which is retinal damage and corneal opacity. This is less common and reversible in case of hydroxychloroquine, which is preferred over chloroquine. Other adverse effects are rashes, graying of hair, irritable bowel syndrome, myopathy and neuropathy.

Chloroquine/hydroxychloroquine are employed in milder nonerosive disease, especially when only one or a few joints are involved, or they are combined with Mtx/sulfasalazine.

Chloroquine 150 mg (base) per day.

Hydroxychloroquine 400 mg/day for 4–6 weeks, followed by 200 mg/day for maintenance.

ZHQUINE, ZYQ 200 mg tab.

4. Leflunomide

This immunomodulator inhibits proliferation of stimulated lymphocytes in patients with active RA. Arthritic symptoms are suppressed and radiological progression of disease is retarded. In clinical trials its efficacy has been rated comparable to Mtx and onset of benefit is as fast (4 weeks).

Leflunomide is rapidly converted in the body to an active metabolite which inhibits *dihydroorotate dehydrogenase* and pyrimidine synthesis in actively dividing cells. Antibody production by B-cells may be depressed. The active metabolite has a long t½ of 2–3 weeks; leflunomide, therefore, is given in a loading dose of 100 mg daily for 3 days followed by 20 mg OD.

Adverse effects of leflunomide are diarrhoea, headache, nausea, rashes, loss of hair, thrombocytopenia, leucopenia, increased chances of chest infection and raised hepatic transaminases. It is not to be used in children and pregnant/lactating women. Leflunomide is an alternative to Mtx or can be added to it, but the combination is more hepatotoxic. Combination with sulfasalazine improves benefit.

LEFRA 10 mg, 20 mg tabs.

Gold Injected i.m. as gold sodium thiomalate, gold is the oldest drug capable of arresting progression of RA. Because of high toxicity (hypertension, dermatitis, stomatitis, kidney/liver/bone marrow damage) it has gone out of use. *Auranofin* the orally active gold compound is less effective and less toxic (causes diarrhoea, abdominal cramps etc.), but has been replaced now by better drugs.

d-Penicillamine It is a copper chelating agent (*see* Ch. 66), with a gold like action in RA. Toxicity is also similar and it is no longer used in this disease.

Biological agents

Recently, several recombinant proteins/monoclonal antibodies that bind and inhibit cytokines, especially TNFα or IL-1 have been produced and found to afford substantial benefit in autoimmune diseases like RA, inflammatory bowel diseases, psoriasis, scleroderma, etc. All of them produce prominent adverse effects, are expensive, and are used only as reserve drugs for severe refractory disease.

TNFα inhibitors

Because TNFα plays a key role in the inflammatory cascade of RA by activating membrane bound receptors ($TNFR_1$ and $TNFR_2$) on the surface of T-cells, macrophages, etc., exogenously administered soluble TNF-receptor protein or antibody can neutralize it and interrupt the reaction. TNF inhibitors mainly suppress macrophage and T-cell function; inflammatory changes in the joint regress and new erosions are slowed. Quicker response than nonbiologic DMARDs has been obtained. Though effective as monotherapy, they are generally added to Mtx when response to the latter is not adequate or in rapidly progressing cases. Susceptibility to opportunistic infections, including tuberculosis and pneumocystis pneumonia is increased.

Etanercept: It is a recombinant fusion protein of TNF-receptor and Fc portion of human IgG_1; administered by s.c. injection 50 mg weekly. Pain, redness, itching and swelling occur at injection site and chest infections may be increased, but immunogenicity is not a clinical problem.

Dose: 25–50 mg s.c. once or twice weekly;
ENBREL, ENBROL 25 mg in 0.5 ml, 50 mg in 1 ml inj.

Infliximab: It is a chimeral monoclonal antibody which binds and neutralizes TNFα; 3–5 mg/kg is infused i.v. every 4–8 weeks. An acute reaction comprising of fever, chills, urticaria, bronchospasm, rarely anaphylaxis may follow the infusion. Susceptibility to respiratory infections is increased and worsening of CHF has been noted. It is usually combined with Mtx which improves the response and decreases antibody formation against infliximab.

Adalimumab: This recombinant monoclonal anti-TNF antibody is administered s.c. 40 mg every 2 weeks. Injection site reaction and respiratory infections are the common adverse effects. Combination with Mtx is advised to improve the response and decrease antibody formation.

IL-1 antagonist

Anakinra: It is a recombinant human IL-1 receptor antagonist. Though clinically less effective than TNF inhibitors, it has been used in cases who have failed on one or more DMARDs.
Dose: 100 mg s.c. daily.
Local reaction and chest infections are the main adverse effects.

Abatacept which inhibits T-cell activation, and *Rituximab* a monoclonal antibody that destroys and depletes B-cells, are other newer biologicals being used in refractory RA.

8. Corticosteroids (*see* Ch. 20)

Glucocorticoids have potent immunosuppressant and antiinflammatory activity: can be inducted almost at any stage in RA along with first or second line drugs, if potent antiinflammatory action is required while continuing the NSAID ± DMARD. Symptomatic releif is prompt and marked but they do not arrest the rheumatoid process, though joint destruction may be slowed and bony erosions delayed.

Long-term use of corticosteroids carries serious disadvantages. Therefore,

- either low doses (5–10 mg prednisolone or equivalent) are used to supplement NSAIDs (once used in this manner, it is difficult to withdraw the steroid—exacerbation is mostly precipitated and the patient becomes steroid dependent)
- or high doses are employed over short periods in cases with severe systemic manifestations (organ-threatening disease, vasculitis) while the patient awaits response from a remission inducing drug.

In cases with single or a few joint involvement with severe symptoms, intraarticular injection of a soluble glucocorticoid affords relief for several weeks; joint damage may be slowed. This procedure should not be repeated before 4–6 months.

DRUGS USED IN GOUT

Gout It is a metabolic disorder characterized by hyperuricaemia (normal plasma urate 2–6 mg/dl). Uric acid, a product of purine metabolism, has low water solubility, especially at low pH. When blood levels are high, it precipitates and deposits in joints, kidney and subcutaneous tissue (tophy).

Secondary hyperuricaemia occurs in:

(a) Leukaemias, lymphomas, polycythaemia—especially when treated with chemotherapy or radiation: due to enhanced nucleic acid metabolism and uric acid production.

(b) Drug induced—thiazides, furosemide, pyrazinamide, ethambutol, levodopa reduce uric acid excretion by kidney.

Drugs used in gout are:

For acute gout

NSAIDs
Colchicine
Corticosteroids

For chronic gout/hyperuricaemia

Uricosurics	*Synthesis inhibitors*
Probenecid	Allopurinol
Sulfinpyrazone	Febuxostat

ACUTE GOUT

Acute gout manifests as sudden onset of severe inflammation in a small joint (commonest is metatarso-phalangeal joint of great toe) due to precipitation of urate crystals in the joint space. The joint becomes red, swollen and extremely painful: requires immediate treatment.

1. NSAIDs

One of the strong antiinflammatory drugs, e.g. *naproxen, piroxicam, diclofenac, indomethacin* or *etoricoxib* is given in relatively high and quickly repeated doses. They are quite effective in terminating the attack, but may take 12–24 hours, i.e. response is somewhat slower than with colchicine, but they are generally better tolerated; majority of patients prefer them over colchicine. Their strong antiinflammatory (not uricosuric) action is responsible for the benefit. Naproxen and piroxicam specifically inhibit chemotactic migration of leucocytes into the inflamed joint. After the attack is over, they may be continued at lower doses for 3–4 weeks while drugs to control hyperuricaemia take effect. They are not recommended for long term management due to risk of toxicity.

The NSAIDs have also substituted colchicine for covering up the period of initiation of therapy (6–8 weeks) with allopurinol or uricosurics in chronic gout.

2. Colchicine

It is an alkaloid from *Colchicum autumnale* which was used in gout since 1763. The pure alkaloid was isolated in 1820.

Colchicine is neither analgesic nor anti-inflammatory, but it specifically suppresses gouty inflammation. It does not inhibit the synthesis or promote the excretion of uric acid. Thus, it has no effect on blood uric acid levels.

An acute attack of gout is started by the precipitation of urate crystals in the synovial fluid. On being engulfed by the synovial cells, they release mediators and start an inflammatory response. Chemotactic factors are produced → granulocyte migration into the joint; they phagocytose urate crystals and release a glycoprotein which aggravates the inflammation by:

(i) Increasing lactic acid production from inflammatory cells → local pH is reduced → more urate crystals are precipitated in the affected joint.

(ii) Releasing lysosomal enzymes which cause joint destruction.

Colchicine does not affect phagocytosis of urate crystals, but inhibits release of chemotactic factors and of the glycoprotein, thus suppressing the subsequent events. By binding to fibrillar protein tubulin, it inhibits granulocyte migration into the inflamed joint and thus interrupts the vicious cycle. Other actions of colchicine are:

(a) Antimitotic: causes metaphase arrest by binding to microtubules of mitotic spindle. It was tried for cancer chemotherapy but abandoned due to toxicity. It is used to produce polyploidy in plants.

(b) Increases gut motility through neural mechanisms.

Pharmacokinetics Colchicine is rapidly absorbed orally, partly metabolized in liver and excreted in bile—undergoes enterohepatic circulation; ultimate disposal occurs in urine and faeces over many days. Binding of colchicine to intracellular tubulin contributes to its large volume of distribution and slow elimination. Inhibitors of CYP3A4 retard colchicine metabolism and enhance its toxicity.

Toxicity is high and dose related.

Nausea, vomiting, watery or bloody diarrhoea and abdominal cramps occur as dose limiting adverse effects. Accumulation of the drug in intestine and inhibition of mitosis in its rapid turnover mucosa is responsible for the toxicity. In overdose, colchicine produces kidney damage, CNS depression, intestinal bleeding; death is due to muscular paralysis and respiratory failure.

Chronic therapy with colchicine is not recommended because it causes aplastic anaemia, agranulocytosis, myopathy and loss of hair.

Use

(a) *Treatment of acute gout* Colchicine is the fastest acting drug to control an acute attack of gout; 0.5 mg 1–3 hourly with a total of 3 doses in a day; maximum 6.0 mg in a course spread over 3–4 days. Control of attack is usually achieved in 4–12 hours. A second course should not be started before 3–7 days. The response is dramatic, so much so that it may be considered diagnostic. However, because of higher toxicity, it is used only when NSAIDs are ineffective or cannot be used. Maintenance doses (0.5–1 mg/day) may be given for 4–8 weeks in which time control of hyperuricaemia is achieved with other drugs.

(b) *Prophylaxis* Colchicine 0.5–1 mg/day can prevent further attacks of acute gout, but NSAIDs are generally preferred.

Taken at the first symptom of an attack, small doses (0.5–1.5 mg) of colchicine abort it.

ZYCOLCHIN, GOUTNIL 0.5 mg tab.

3. Corticosteroids

Intraarticular injection of a soluble steroid suppresses symptoms of acute gout. Crystalline preparations should not be used. It is indicated in refractory cases and those not tolerating NSAIDs/colchicine.

Systemic steroids are rarely needed. They are highly effective and produce nearly as rapid a response as colchicine, but are reserved for patients with renal failure/history of peptic ulcer

bleed in whom NSAIDs are contraindicated or for cases not responding to or not tolerating NSAIDs. Prednisolone 40–60 mg may be given in one day, followed by tapering doses over few weeks.

CHRONIC GOUT

When pain and stiffness persist in a joint between attacks, gout has become chronic. Other cardinal features are hyperuricaemia, tophi (chalk-like stones under the skin in pinna, eyelids, nose, around joints and other places) and urate stones in the kidney. In majority of patients, hyperuricaemia is due to undersecretion of uric acid, while in few it is due to over production. Chronic gouty arthritis may cause progressive disability and permanent deformities.

A. URICOSURIC DRUGS

1. Probenecid

It is a highly lipid-soluble organic acid developed in 1951 to inhibit renal tubular secretion of penicillin so that its duration of action could be prolonged. It competitively blocks active transport of organic acids by OATP at all sites; that in renal tubules being the most prominent. This transport is bidirectional: net effect depends on whether secretion or reabsorption of the particular organic acid is quantitatively more important, e.g.:
(a) Penicillin is predominantly secreted by the proximal tubules, its reabsorption is minimal. Net effect of probenecid is inhibition of penicillin excretion; more sustained blood levels are achieved.
(b) Uric acid is largely reabsorbed by active transport, while less of it is secreted; only 1/10th of the filtered load is excreted in urine. The major transporter involved is URAT-1, a member of the OATP family. Probenecid, therefore, promotes uric acid excretion and lowers its blood level.

Probenecid does not have any other significant pharmacological action; it is neither analgesic nor antiinflammatory.

Interactions

1. In addition to penicillins, probenecid inhibits the urinary excretion of cephalosporins, sulfonamides, Mtx and indomethacin.
2. It inhibits biliary excretion of rifampicin. Pyrazinamide and ethambutol may interfere with uricosuric action of probenecid.
3. Probenecid inhibits tubular secretion of nitrofurantoin which may not attain antibacterial concentration in urine.
4. Salicylates block uricosuric action of probenecid.

Pharmacokinetics Probenecid is completely absorbed orally; 90% plasma protein bound: partly conjugated in liver and excreted by the kidney; plasma t½ is 6–8 hours.

Adverse effects Probenecid is generally well tolerated.
Dispepsia is the most common side effect (upto 25% incidence with high doses). It should be used cautiously in peptic ulcer patients. Rashes and other hypersensitivity phenomena are rare. Toxic doses cause convulsions and respiratory failure.

Uses

1. Chronic gout and hyperuricaemia: Probenecid is a second line/adjuvant drug to allopurinol. Started at 0.25 g BD and increased to 0.5 g BD, it gradually lowers blood urate level; arthritis, tophi and other lesions may take months to resolve. Colchicine/NSAID cover is advised during the initial 1–2 months to avoid precipitation of acute gout.

Probenecid and other uricosurics are ineffective in the presence of renal insufficiency (serum creatinine > 2 mg/dl). Plenty of fluids should be given with probenecid to avoid urate crystallization in urinary tract.

2. Probenecid is also used to prolong penicillin or ampicillin action by enhancing and sustaining their blood levels, e.g. in gonorrhoea, SABE.

3. Probenecid is given along with cidofovir, a drug for CMV retinitis in AIDS patients, to prevent its nephrotoxicity.

BENEMID, BENCID 0.5 g tab.

2. Sulfinpyrazone

It is a pyrazolone derivative, related to phenylbutazone, having uricosuric action, but is neither analgesic nor anti-inflammatory. It inhibits tubular reabsorption of uric acid, but smaller doses can decrease urate excretion as do small doses of probenecid. Though equally efficacious as probenecid, sulfinpyrazone has gone into disuse because of more gastric irritation and other side effects. It has been withdrawn in USA. Sulfinpyrazone inhibits platelet aggregation as well.

Benzbromarone is another uricosuric drug with restricted use due to hepatotoxicity.

B. URIC ACID SYNTHESIS INHIBITORS

Allopurinol

This hypoxanthine analogue was synthesized as a purine antimetabolite for cancer chemotherapy. However, it had no antineoplastic activity but was a substrate as well as inhibitor of *xanthine oxidase*, the enzyme responsible for uric acid synthesis (Fig. 15.1).

Allopurinol itself is a short-acting (t½ 2 hrs) competitive inhibitor of xanthine oxidase, but its major metabolite *alloxanthine (oxypurine)* is a long-acting (t½ 24 hrs) and noncompetitive inhibitor—primarily responsible for uric acid synthesis inhibition *in vivo*. At high concentrations, allopurinol also becomes noncompetitive inhibitor. During allopurinol administration, plasma concentration of uric acid is reduced and that of hypoxanthine and xanthine is somewhat increased. In place of uric acid alone, all 3 oxipurines are excreted in urine. Since xanthine and hypoxanthine are more soluble, have a higher renal clearance than that of uric acid and each has its individual solubility, precipitation and crystallization in tissues and urine does not occur.

Because of raised levels of xanthine and hypoxanthine, some feedback inhibition of *de novo* purine synthesis and reutilization of metabolically derived purine also occurs.

Pharmacokinetics About 80% of orally administered allopurinol is absorbed. It is not bound to plasma proteins; metabolized largely to alloxanthine. During chronic medication, it inhibits its own metabolism and about 1/3rd is excreted unchanged, the rest as alloxanthine.

Interactions

(a) Allopurinol inhibits the degradation of 6-mercaptopurine and azathioprine: their doses should be reduced to 1/3rd, but not that of thioguanine, because it follows a different metabolic path (S-methylation).

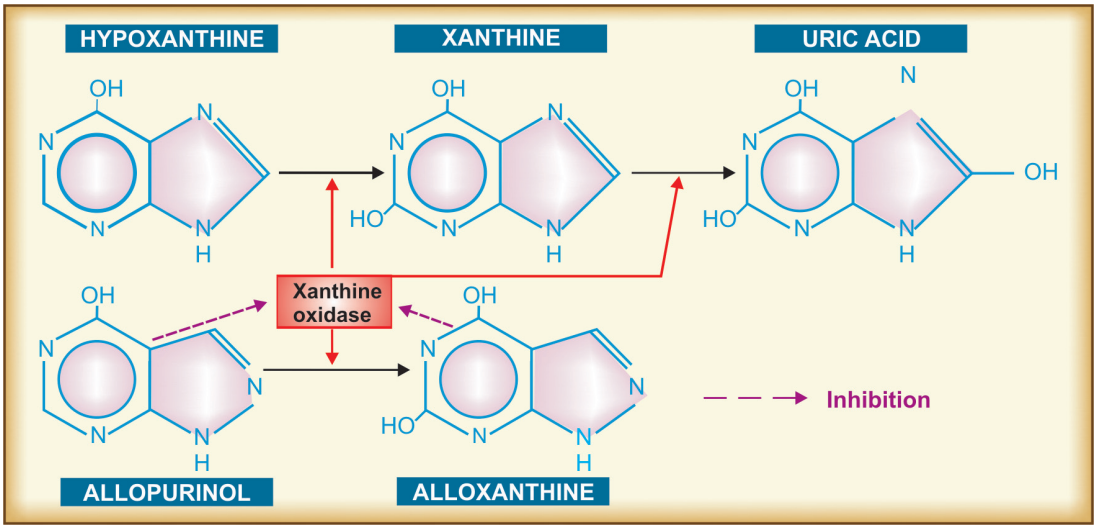


Fig. 15.1: Uric acid synthesis and the action of allopurinol

(b) Probenecid given with allopurinol has complex interaction; while probenecid shortens t½ of alloxanthine, allopurinol prolongs t½ of probenecid.
(c) Allopurinol can potentiate warfarin and theophylline by inhibiting their metabolism.
(d) A higher incidence of skin rashes has been reported when ampicillin is given to patients on allopurinol.

Adverse effects These are uncommon.
Hypersensitivity reaction consisting of rashes, fever, malaise and muscle pain is the most frequent. It subsides on stopping the drug. Renal impairment increases the incidence of rashes and other reactions to allopurinol.
Stevens-Johnson syndrome is a rare but serious risk.
Gastric irritation, headache, nausea and dizziness are infrequent; do not need withdrawal.
Liver damage is rare.

Precautions and contraindications Liberal fluid intake is advocated during allopurinol therapy. It is contraindicated in hypersensitive patients, during pregnancy and lactation.
It should be cautiously used in the elderly, children and in patients with kidney or liver disease.

Uses Allopurinol is the first choice drug in *chronic gout*. It can be used in both *over producers* and *under excretors* of uric acid, particularly more severe cases, with tophi or nephropathy. Uricosurics are infrequently used in India; they are less effective when g.f.r. is low and are inappropriate in stone formers. The two classes of drugs can also be used together when the body load of urate is large.

With long-term allopurinol therapy, tophi gradually disappear and nephropathy is halted, even reversed.

Secondary hyperuricaemia due to cancer chemotherapy/radiation/thiazides or other drugs: can be controlled by allopurinol. It can even be used prophylactically in these situations.

To potentiate 6-mercaptopurine or azathioprine in cancer chemotherapy and immunosuppressant therapy.

Dose: Start with 100 mg OD, gradually increase as needed to 300 mg/day; maximum 600 mg/day.
ZYLORIC 100, 300 mg tabs., ZYLOPRIM, CIPLORIC 100 mg cap.

Caution Allopurinol as well as uricosurics should not be started during acute attack of gout. During the initial 1–2 months of treatment with these drugs, attacks of acute gout are more common—probably due to fluctuating plasma urate levels favouring intermittent solubilization and recrystallization in joints; cover with NSAIDs/colchicine should be provided.

Kala-azar Allopurinol inhibits *Leishmania* by altering its purine metabolism. It was tried as adjuvant to sodium stibogluconate, but abandoned due to poor efficacy.

Febuxostat

It is a recently introduced nonpurine xanthine oxidase inhibitor, equally or more effective than allopurinol in lowering blood uric acid level in patients with hyperuricaemia and gout. It is rapidly absorbed orally, highly plasma protein bound, oxidized as well as glucuronide conjugated in the liver and excreted by kidney; the plasma t½ is ~ 6 hours.

The most important adverse effect is liver damage; liver function needs to be monitored during febuxostat therapy. Diarrhoea, nausea and headache are the usual side effects. By inhibiting xanthine oxidase, it has the potential to interact with mercaptopurine, azathioprine and theophylline; should not be given to patients receiving these drugs.

Febuxostat is an alternative drug for treating symptomatic gout only in patients intolerant to allopurinol, or in those with some contraindications. It is not indicated in malignancy associated hyperuricaemia. Like other drugs used to treat hyperuricaemia, NSAID/colchicine cover should be provided for 1–2 months while initiating febuxostat therapy.

Dose: 40–80 mg OD.
FABULAS, FABUSTAT, ZURIG 40,80,120 mg tabs.

Rasburicase It is a new recombinant xanthine oxidase enzyme that oxidizes uric acid to soluble and easily excreted allantoin. It is indicated only for preventing chemotherapy associated hyperuricaemia when massive lysis of leukaemic or solid tumor mass is induced by cytotoxic drugs in children.