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Nonoral Medication

The possible routes of drug administration are divided into two classes, enteral and parenteral. The enteral routes include sublingual or buccal, oral, and rectal administration. There are many parenteral routes. The most common are intravenous, intramuscular, and subcutaneous injections, inhalation, and topical applications to the skin, eyes, or certain mucous membranes. Drug absorption from these sites is determined by the physicochemical properties of the drug, the dosage form, and certain physiologic and anatomic factors. This chapter concerns some of the more important biopharmaceutic and pharmacokinetic principles that must be considered when a drug is administered by nonoral routes.

INTRAVENOUS INJECTION

Injection into a peripheral vein is the most common method of directly introducing a drug into the systemic circulation. Intravenous administration is used when a rapid clinical response is required, as in the treatment of epileptic seizures, acute asthmatic episodes, dangerously elevated or dangerously low blood pressure, or life-threatening arrhythmias. This route permits precise dosing that can result in predictable drug concentrations in the plasma.

Most drug solutions should be injected over a 1- to 2-min period or longer to avoid excessively high drug concentrations in the blood and other highly perfused tissues immediately following the injection. Although the initially high concentrations following a rapid iv injection are transient, they can produce local pain and undesirable cardiovascular and central effects. Serious clinical problems have resulted from too rapid injection of phenytoin. The usual intravenous loading dose (10 to 20 mg/kg) or maintenance dose (100 mg every 6 to 8 hr) of phenytoin sodium should be injected at a rate not exceeding 50 mg/min.

Insoluble materials, such as drug suspensions, cannot be given by intravenous injection because they may cause embolism. There may also be a danger of precipitation of a drug in the vein resulting in thrombophlebitis if a drug solution is injected too rapidly. Consequently, the manufacturer of injectable diazepam, which is used as an anticonvulsant in doses of 5 to 10 mg, directs that "when used intravenously the solution should be injected slowly, directly into the vein, taking at least one minute for each 5 mg given." Diazepam is poorly water-soluble. The injectable product contains the drug dissolved in 40% propylene glycol and 10% ethanol. When this solution is added to saline solution, a precipitate forms immediately. Even when this injection is given slowly there may be local pain due, at least in part, to the solvent.

An alternative solvent for intravenous administration of lipid soluble drugs such as diazepam has been described; the drug is dissolved in the soy bean oil phase of an emulsion. A clinical evaluation of diazepam emulsion given intravenously indicated that in 314 patients only 5% complained of discomfort and 0.3% of pain. In the control group of 63 patients treated with diazepam in the usual propylene glycol solvent, 43% complained of discomfort and 35% of pain after injection.[1]

Patients given repeated courses of cytotoxic drugs require central venous access when peripheral administration is ruled out by inadequate veins. Central access may also be useful for hyperalimentation and for patients with hemophilia and other hematological diseases. Access is usually achieved by using percutaneous catheters, such as the Hickman catheter. This is inconvenient and care is required to avoid sepsis. An alternative, con-

sisting of a total implantable silicone catheter connected to a stainless steel chamber with a silicone injection port, has been described.[2]

Under general or local anesthesia, the catheter is inserted into a central vein through the arm, neck, or groin and connected by a subcutaneous tunnel to the chamber, which is implanted subcutaneously on the chest wall. The chamber must be flushed with heparinized saline solution after each use.

Some drugs, including lidocaine, theophylline, and certain antibiotics, are administered by means of intravenous infusion or drip. Continuous intravenous infusions of opiates are commonly used in intensive care units and for the management of postoperative pain. This method of administration is particularly useful with drugs having short half-lives or narrow therapeutic indices. Still more precise drug delivery can be achieved with an infusion pump. This controlled approach is needed with drugs like oxytocin, nitroglycerin, alfentanyl, esmolol, or dopamine which are rapidly metabolized.

To avoid the delay in reaching steady state, intravenous infusions are often preceded by a loading dose. Some of the dosing schemes are quite complicated. An example is found in a study concerned with the efficacy and safety of an intravenous dosage regimen of disopyramide in ventricular arrhythmias in patients with at least four premature ventricular contractions (PVCs) per minute.[3] Disopyramide was injected intravenously at a rate of 0.5 mg/kg over 5 min. Each patient received two or three additional loading doses during the first hour with at least 5-min intervals between them. Intravenous infusion was started with the first divided loading dose and continued at a rate of 1 mg/kg/hr for 3 hr and at 0.4 mg/kg/hr for an additional 15 hr. In 8 of 10 patients the frequency of PVCs fell by at least 70% and the response persisted during the continuous infusion.

A pharmacokinetic model of distribution and elimination, and the average drug concentration needed to maintain sleep were used to devise a dosing regimen for etomidate, a short-acting intravenous anesthetic agent.[4] The complex pharmacokinetic profile of etomidate (three-compartment open model) and its rapid elimination (clearance = 1200 ml/min) prompted the development of a three-step intravenous infusion regimen to satisfy the clinical requirements. Etomidate was given according to the following protocol: 0.1 mg/kg per min for 3 min, 0.02 mg/kg for 27 min, and 0.01 mg/kg for the remainder of the procedure.

The eyelid reflex disappeared about 2 min after the start of the first infusion. Anesthesia was considered clinically satisfactory in all cases and no important side effects were observed during maintenance or recovery. Nine of the 11 patients awoke within 10 min of stopping etomidate. A three-stage iv infusion dosing regimen to suppress ventricular ectopic depolarizations has also been described for flecainide.[5]

Sometimes, the administration of a drug as a continuous iv infusion appears to have clear advantages over intermittent treatment. For example, Hull et al.[6] compared continuous iv heparin with intermittent subcutaneous heparin (every 12 hr) in the initial treatment of patients with acute proximal deep-vein thrombosis. Intermittent subcutaneous treatment was inferior to continuous iv heparin in preventing recurrent venous thromboembolism. The incidence of recurrence was about 20% for the subcutaneous group and 5% for the iv infusion group.

Daily fluctuations in motor performance, frequently accompanied by dyskinesias, are one of the most common problems in patients with Parkinson's disease after long-term treatment with intermittent oral levodopa. Continuous iv infusions of levodopa have been found to correct random on-off fluctuations.[7] Constant plasma concentrations of levodopa produce a constant response for prolonged periods of time.

Patients with cancer treated with cisplatin are given metoclopramide to control nausea and vomiting. Substantial control of emesis (two episodes or fewer) was achieved in about 80% of the patients given continuous metoclopramide compared with about 50% of the patients receiving intermittent metoclopramide.[8]

Adoptive immunotherapy with bolus-dose recombinant interleukin-2 (IL-2) has been reported to induce tumor regression in some patients with cancer, but has been associated with severe fluid retention and other adverse effects. In an effort to preserve the efficacy but reduce the toxicity of this treatment, West et al.[9] used escalating doses of IL-2 as a constant iv infusion rather than as a bolus injection.

Response rate among the patients who could be evaluated was similar to the rates observed in earlier studies, which used bolus doses, suggesting that administration of IL-2 as a constant infusion preserved the antineoplastic activity of adoptive immunotherapy. At the same time, this mode of

administration appears to substantially increase the safety and comfort of patients.

One study, using bolus doses of IL-2, found that 16 of 25 patients retained fluid in excess of 10% of total body weight, and 20 of the 25 patients experienced dyspnea. In the infusion study, severe fluid retention occurred in only 5 of 40 patients and pulmonary edema was observed in 6 patients. The investigators conclude that "by permitting the delivery of adoptive cellular therapy in a tolerable and safe manner, the administration of IL-2 as a constant infusion may . . . hasten the day when this form of biotherapy can be integrated into the combined-modality treatment of patients with cancer."

Intravenous infusions sometimes fail because of extravasation of infusate or development of phlebitis. This interferes with therapy, causes considerable patient discomfort, and increases workload for hospital staff. Extravasation and phlebitis may be initiated by venoconstriction in the region of the infusion site brought about by irritation of the endothelium. If this is the case, it may be possible to reduce the frequency of these events by keeping the veins dilated. This might be accomplished with topical nitroglycerin.

Nitroglycerin patches releasing 5 mg/day or placebo patches were applied to the skin of patients distal to intravenous infusion sites in a double-blind manner.[10] The frequency of infusion failure was much lower with the active patch than with placebo. Of the 103 infusions in the placebo group, 44 failed, compared with 15 failures among the 105 infusions in the nitroglycerin group.

When a drug is given intravenously, the amount administered and the rate of administration can be carefully controlled and bioavailability is ordinarily not an issue. The amount reaching the systemic circulation is the amount given. The iv administration of prodrugs, however, is an exception. Certain drugs are modified chemically to produce more water-soluble derivatives for injection. These derivatives frequently have little pharmacologic activity; clinical response depends on conversion to parent drug in the body. A slow rate of conversion could result in poor bioavailability of the active form of the drug.

Relatively few investigations have been directed to this problem. Studies in man indicate that dexamethasone phosphate (an ester prodrug) is rapidly and efficiently converted to dexamethasone after intravenous injection.[11] The overall conversion is approximately 90%, and the half-life of conversion is about 10 min. A different prodrug, dexamethasone sulfate, yields virtually no free dexamethasone in plasma or urine after intravenous injection.[12] About 60% of the dose is recovered in the urine in the form of unchanged dexamethasone sulfate. These results cast serious doubts on the clinical value of this prodrug.

Renal allograft rejections are often treated with large intravenous doses of prednisolone. The solubility of prednisolone, however, is poor and, in the US, it is usually given in the form of a freely soluble prodrug, either prednisolone sodium succinate or prednisolone disodium phosphate (prednisolone phosphate). In other countries, prednisolone tetrahydrophthalate (prednisolone phthalate) is also used.

The time course of hydrolysis of iv doses of prednisolone phosphate and phthalate (to form prednisolone) was studied in renal transplant patients.[13] In all patients, the hydrolysis of the prednisolone phosphate ester was faster than that of the prednisolone phthalate ester. The mean peak concentration of prednisolone was higher for the phosphate than the phthalate (18.5 μg/ml *versus* 2.9 μg/ml). The mean AUCs of prednisolone were 2341 μg/ml/min for the phosphate and 1299 μg/ml/min for the phthalate.

The phosphate ester appeared to be converted to prednisolone very efficiently. On the other hand, about 50% of the iv dose of the phthalate was metabolized and/or excreted before conversion. Therapeutic inequivalence must be expected when patients are treated with equimolar doses of these two prodrugs.

When chloramphenicol is required for intravenous therapy it is given in the form of a sodium salt of the succinate ester. Recent studies indicate that this ester prodrug may present bioavailability problems in certain patients. As much as 40% of the prodrug is recovered unchanged in the urine after intravenous injection to critically ill adult patients.[14] Similar results were found in sick children; bioavailability of chloramphenicol after injection of the succinate ester ranged from 55 to 92%.[15]

INTRA-ARTERIAL ADMINISTRATION

The principal application of this mode of drug administration is in the field of cancer chemotherapy. Liver involvement by metastatic cancer occurs frequently and is a major source of morbidity and mortality. With metastatic colorectal cancer, most

of the tumor may reside in the liver. Infusion of chemotherapeutic agents directly into the hepatic artery can potentially expose the tumor to higher drug concentrations than are possible with conventional intravenous infusions.[16]

Theoretical advantages of intra-arterial drug administration have been described in considerable detail.[17,18] Only a small fraction of the dose of a drug given intravenously may reach the target organ if drug elimination by the lungs and other tissues is significant. Accordingly, drug selection for hepatic arterial administration should include agents with high extrahepatic clearance relative to hepatic blood flow. Under these conditions, exposure of the hepatic tumor to drug is increased relative to the exposure of such sensitive tissues as the bone marrow and gastrointestinal epithelium. Furthermore, if there is extraction of the drug by the liver, even less drug will be delivered systemically. In other words, for a given level of systemic exposure, more regional exposure can be obtained. The achievement of higher drug concentrations in the liver with lower systemic levels should increase local antitumor effects and decrease systemic toxic effects, thereby improving the therapeutic index of treatment.

In 1978, Ensminger et al.[19] evaluated the degree to which hepatic arterial infusion of floxuridine (FUDR) or fluorouracil produces higher hepatic and lower systemic drug concentrations than are achieved with corresponding peripheral venous infusions. Fifteen patients with primary or metastatic liver cancer were studied.

Both drugs are efficiently eliminated by the liver. On hepatic arterial infusion, 94 to 99% of FUDR and 19 to 51% of fluorouracil are extracted in one pass through the liver. The high hepatic extraction of these drugs suggests that infusion of these fluorinated pyrimidines directly into the hepatic artery should produce lower systemic drug concentrations than those obtained when equivalent doses are given by a peripheral vein. With FUDR, hepatic arterial infusion resulted in systemic levels of about 25% of corresponding systemic levels with intravenous infusion. Differences in systemic levels were less dramatic with fluorouracil; systemic levels with hepatic arterial infusion ranged from 50 to 77% of corresponding levels with peripheral vein infusion.

A principal objective of this investigation was to demonstrate higher drug concentrations in the liver and hepatic tumor after hepatic arterial administration than after intravenous administration of equivalent doses. Drug concentration in the hepatic vein was assumed to reflect the concentration prevailing proximally in the tumor blood supply. Hepatic arterial infusion produced hepatic vein levels that were about 2 to 6 times higher than those achieved when FUDR was given by a peripheral route. Hepatic vein levels of fluorouracil were also higher with hepatic arterial than peripheral vein administration, but differences were only in the order of 40 to 60%.

Hepatic tumors derive their blood supply primarily from the hepatic artery. Because only one-third of hepatic blood flow is derived from the hepatic artery, the actual tumor exposure to drug given via the hepatic artery may be two or three times higher than reflected in the hepatic vein levels.

These results generally support hepatic arterial infusion as a means to improve the therapeutic index of FUDR and fluorouracil in the treatment of liver cancer. This hypothesis was tested directly by Kemeny et al.,[20] who compared the efficacy of FUDR given by 14-day continuous infusion via the hepatic artery or cephalic vein in patients with liver metastases from colorectal cancer.

Intrahepatic therapy produced a significantly higher complete or partial response rate than systemic therapy (50% *versus* 20%). Patients randomized to systemic therapy who exhibited tumor progression were then given intrahepatic chemotherapy. About 25% of these patients had a partial response and 33% a minor response or stabilization of disease. The investigators concluded that hepatic arterial chemotherapy significantly increases response rate to FUDR for hepatic metastases from colorectal cancer and appears to be a more effective treatment than systemic chemotherapy.

Controlling Hepatic Blood Flow Rate

If the extrahepatic clearance of a drug is relatively high, the concentration of drug in the liver and hepatic tumor is dependent on the blood flow rate through the hepatic artery. A low arterial blood flow rate will ensure a high local drug level. Several methods have been evaluated to decrease hepatic arterial blood flow, including ligation of the hepatic artery, the use of balloon catheters, the infusion of vasoconstrictors such as epinephrine or vasopressin, and the use of biodegradable microspheres.[16]

Hepatic arterial injection of degradable starch microspheres, approximately 40-μm diameter, can

produce transient, nearly complete blockage of blood through the hepatic arterial bed. Blood flow resumes in 15 to 30 min as the microspheres are digested by serum amylase. The hepatic arterial injection of a suspension of starch microspheres in a drug solution could temporarily retain the drug in the hepatic arterial capillary bed, resulting in higher drug concentrations in the surrounding tissue. When the antineoplastic drug carmustine (BCNU) is given with starch microspheres directly into the hepatic artery, systemic drug exposure is reduced up to 90% compared to the exposure when drug is injected alone, because of increased drug delivery to the liver and hepatic tumor.[16]

Gyves et al.[21] examined the potential for decreased systemic exposure to mitomycin by concurrent hepatic arterial injection of starch microspheres. Mitomycin was selected because it has activity against several tumors that metastasize to the liver, its dose is limited by myelosuppression when given systemically, and it has a high total body clearance.

Mitomycin (10 mg/m^2) was given via the hepatic artery to patients with incurable liver tumors, alone or with starch microspheres (36 or 90 million). Mitomycin concentrations were measured in plasma over the next 60 min.

Both doses of starch microspheres significantly reduced systemic exposure to mitomycin after hepatic arterial administration. At the lower dose, the microspheres reduced the average systemic exposure to mitomycin by 33%, with individual values ranging from 18 to 52%. At the higher dose of microspheres, the average reduction in systemic exposure was 40%, with a range of 17 to 72%.

The failure to observe a larger effect on mitomycin at the higher dose of microspheres than at the lower dose is surprising, but studies on hepatic blood flow distribution after administration of starch microspheres provide insight. In some patients, temporary arterial venous shunts develop within the liver during blockage of the arteriolar capillary bed by microspheres. The degree of intrahepatic shunting appears to be related to the dose of degradable starch microspheres. Arterial venous shunting reduces the effectiveness of the microspheres because drug in the shunted blood evades hepatic extraction and is available to the systemic circulation.

The effect of degradable starch microspheres on the pharmacokinetics of intrahepatic floxuridine and mitomycin was studied in patients with colon carcinoma metastatic to the liver.[22] The biodegradable microspheres decreased arterial blood flow to normal liver by about two-thirds and to hepatic tumor by nearly 80%. The microspheres reduced systemic (plasma) exposure to floxuridine by one-third and to mitomycin by 20%. The estimated increase in tumor exposure produced by the starch microspheres was nearly 4-fold for floxuridine and 3-fold for mitomycin.

The principal effect of degradable starch microspheres is a widening of the therapeutic window—the same degree of tumor exposure results in less systemic exposure. The investigators suggest that the search for agents that might lend themselves to the successful exploitation of this approach might best start with a re-examination of drugs that have demonstrated activity in pre-clinical trials but proved too toxic for clinical use.

Treating Brain Tumors—Some Potential Problems

Intra-arterial administration of antineoplastic drugs for the treatment of malignant gliomas, metastatic tumors, and primary lymphomas in the brain is also under investigation, but focal toxicity remains a problem. The most frequently reported local toxicity is retinal damage.

A possible cause of focal tissue damage is nonuniform drug delivery related to incomplete mixing. A key assumption underlying pharmacokinetic theory of arterial drug administration is that mixing is complete before the first distal arterial branch. This may not be the case, particularly if the infusion rate is much lower than blood flow rate.

According to Blacklock et al.,[23] at low infusion rates, the solution emerges from the catheter tip as a thin stream that remains stable for some distance and exits in variable concentrations into arterial branches. At higher infusion rates, the infused jet is unstable and tends to mix with the blood near the site of infusion.

These investigators studied brain distribution of labeled iodoantipyrine in monkeys after internal carotid artery infusion at slow infusion rates (1 to 2% of arterial blood flow) and fast infusion rates (20% of blood flow). The deposition of isotope in the infused hemisphere after slow infusion was strikingly heterogeneous, with as much as 13-fold differences in drug concentration in anatomically contiguous areas of the brain. Animals that were given fast intra-arterial infusions, designed to pro-

mote drug mixing, had much more uniform drug deposition in the perfused hemisphere.

Blacklock and his colleagues believe that the cause of heterogeneous distribution is drug streaming in the internal carotid artery and its branches. They note that "a variable delivery of antineoplastic agents to the perfused tissue . . . may result in subtherapeutic drug levels at sites containing tumor and toxic levels at other sites within the perfused hemisphere. Drug streaming during intra-arterial infusion may be the cause of the focal cerebral toxicity currently being observed in patients who received intracarotid chemotherapy."

Dedrick[24] suggests that drug streaming may also be a problem for intrahepatic arterial administration. Hepatic arterial infusion of floxuridine has produced considerable local toxicity (e.g., intestinal ulcers, biliary sclerosis) not seen with systemic administration. This may due to drug streaming. Dedrick concluded that "it would be prudent to consider suitable techniques, such as pulsing or jetting the infusate, to attempt to eliminate or reduce the potential problem." The efficacy and safety of intra-arterial chemotherapy cannot be evaluated until intravascular drug streaming is eliminated as a confounding factor in clinical trials.

SPINAL ADMINISTRATION

Many drugs do not easily penetrate the blood-brain barrier; systemic administration results in low and ineffective drug concentrations in cerebrospinal fluid (CSF). An alternative route for the administration of antibiotics, antifungals, or antineoplastics, which may be required for life-threatening situations, is direct injection into the CSF. This is usually accomplished by lumbar puncture and injection into the subarachnoid space. A comprehensive review of intrathecal drug therapy was published in 1978.[25]

Spinal administration of opiates was first considered about 10 yr ago. Opioid receptors are present at several sites in the spinal cord. An intrathecal injection of morphine 0.5 mg delivers far more drug to these spinal receptors than does a much larger, probably lethal, dose of morphine given by iv injection. Disappointingly, this does not result in a more profound degree of analgesia but does provide a more persistent effect. A single dose of intrathecal morphine produces analgesia for 12 to 24 hr in patients who have not previously received opiates. Intrathecal morphine is often used in conjunction with local anesthetics in spinal anesthesia.

Epidural administration of opiates provides a major advantage over intrathecal administration in that the use of an epidural cannula allows for repeat injections or continuous infusion to sustain analgesia.[26] The most important distinction between the epidural and intrathecal routes is the extent to which drug in the epidural space is transferred to the intrathecal rather than the systemic circulation. Several studies have found that morphine but not other opiates is preferentially transferred to the cerebrospinal fluid after subdural administration.

Nordberg et al.[27] investigated the pharmacokinetics of epidural morphine in plasma and cerebrospinal fluid (CSF) in patients undergoing elective thoracotomy for pulmonary tumor. Patients received 2, 4, or 6 mg of morphine administered epidurally (at the lumbar level) within 3 hr after surgery. Morphine was absorbed rapidly from the epidural space; peak plasma concentrations were 20 to 40 ng/ml, comparable to the levels found after intramuscular injection of morphine, and occurred within 15 min after administration. The half-life of morphine in plasma averaged about 3 hr. Cerebrospinal fluid concentration of morphine was 50 to 200 times higher than morphine concentration in plasma throughout the 5-hr period of study. Because of the high CSF/plasma concentration ratio, CSF morphine levels were substantial even 20 hr after epidural injection.

The mean duration of analgesia (the time interval between the epidural morphine dose and the first intramuscular injection of meperidine) increased with increasing epidural doses, ranging from 8.6 hr after the 2-mg dose to 15.6 hr after the 6-mg dose. In the group receiving the 6-mg dose, the respiratory rate tended to decrease after injection.

In another study, 33 patients were randomly assigned to two groups to study the analgesic potency, duration of action, and side effects of epidurally and intramuscularly administered morphine after hip surgery.[28] An epidural injection of 10 ml of normal saline solution containing 2 mg morphine was given to one group, and a 10-mg intramuscular injection of morphine was given to the other.

There was a more rapid onset of action after intramuscularly injected morphine (less than 15 min in all patients) than after epidurally injected morphine (15 to 60 min). However, the degree of pain relief was substantially greater and the duration of action markedly longer after epidurally administered morphine than after intramuscularly administered morphine. On the average, an additional

21 mg of intramuscularly administered morphine was required to maintain analgesia in the first group during the 15-hr observation period, whereas only an additional 1.6 mg of epidurally administered morphine was required in the second group. Five of 15 patients who received morphine epidurally required no additional analgesia after the initial dose, compared with only 1 of 18 patients given morphine intramuscularly.

Carmichael et al.[29] carried out a randomized, double-blind, placebo-controlled study of the efficacy, duration, and safety of epidurally administered morphine for the management of pain after cesarean section. Three groups of patients received either 0, 4, or 8 mg morphine sulfate in 10 ml of normal saline solution through an epidural catheter at the completion of the operation.

Compared with the saline solution controls, both groups receiving morphine epidurally had significantly greater pain relief, a longer time to the first administration of additional analgesic, and a decreased amount of supplemental analgesia required in the first 36 hr after surgery. The average time to the first administration of an additional analgesic drug was 2.8 hr for the group receiving saline solution, 22.5 hr for the group receiving 4 mg of morphine, and 26.5 hr for the group receiving 8 mg of morphine. The average numbers of supplemental analgesic doses over the 36-hr period were 11.5 for the group receiving saline solution, 2.6 for the group receiving 4 mg of morphine and 1.8 for the group receiving 8 mg of morphine.

Some clinicians have found that the duration of analgesia from a single dose of epidural morphine is insufficient and have favored continuous epidural infusion. El-Baz et al.[30] evaluated postoperative pain relief and the incidence of side effects in patients given either intermittent epidural injection of morphine as needed or continuous epidural morphine supplemented with iv morphine on request. Postoperative pain relief was similar with both methods.

Intermittent epidural injection of morphine relieved pain for an average of 5.8 hr per injection, but was associated with urinary retention in all 30 patients, with pruritus in 12, and with respiratory depression in 8. Continuous epidural infusion of morphine, with occasional iv morphine supplementation, was associated with minimal adverse effects. One patient complained of pruritus and two patients developed urinary retention.

There is also interest in the use of continuous epidural morphine in conjunction with patient-controlled or on-demand analgesia. In one study,[31] patients who underwent abdominal surgery were given 2 mg morphine through an epidural catheter. Following this bolus, a 0.25% solution of morphine HCl was infused at a basal rate of 0.06 ml/hr (equivalent to 0.16 mg morphine per hr). This basal infusion was tapered to zero over several days.

Mean morphine consumption was 4.8 mg on the day of surgery, 1.9 mg on the first postoperative day, and 0.6 mg on the second postoperative day. Satisfactory analgesia was obtained in all patients. A fixed regimen of morphine probably would have required more drug and produced less satisfactory analgesia.

INTRAPERITONEAL ADMINISTRATION

The poor response to chemotherapy in patients with malignant disease of the gastrointestinal tract has prompted efforts to develop alternative techniques for administering therapy. Direct delivery of drug into an area of the body with cancer (regional therapy) is one such approach. The idea behind regional chemotherapy is to provide a pharmacokinetic advantage through high local concentrations of drug, with substantially lower systemic exposure to the drug. Intrahepatic artery treatment of carcinoma of the colon metastatic to the liver, described earlier, is an example of regional therapy.

Another example is the intraperitoneal (IP) administration of antineoplastic drugs as therapy for tumors principally confined to the abdominal cavity.[32] Pharmacokinetic theory predicts that a large and potentially advantageous difference in drug concentration occurs between the peritoneal cavity and the plasma after certain anticancer drugs are given intraperitoneally in large volume.[33]

The rate of removal of a drug from the abdominal cavity will greatly influence the difference in exposure between the cavity and the systemic circulation. Large, water-soluble, and ionized molecules will exit more slowly than smaller, lipid-soluble molecules and demonstrate larger differentials in concentration.

Dedrick[33] points out that when mannitol is given to rats intraperitoneally, the drug concentration in the peritoneal cavity falls with time, while the plasma concentration increases transiently, reaches a peak, and then begins to fall more or less in parallel with the peritoneal concentration, but at about a 10-fold lower value of concentration. This

pattern may be expected with any hydrophilic drug given intraperitoneally.

A major exit mechanism for drugs from the peritoneal cavity is by way of the portal circulation. Systemic exposure after IP administration of drugs subject to extensive first-pass hepatic metabolism will be much lower than predicted by diffusion theory alone. 5-Fluorouracil (5-FU), the most useful drug in the treatment of malignant disease of the GI tract, is extensively metabolized in the liver during its first passage through this organ.

A constant intraperitoneal 5-FU infusion by means of a totally implanted pump system has also been described.[34] In this study, 5 patients received one or more courses of 5-day continuous IP therapy. In each course, a 100 to 1,000 concentration differential in favor of the peritoneal cavity was maintained. Steady-state venous plasma 5-FU concentrations averaged 0.34 μM, whereas steady-state peritoneal levels average 697 μM.

A clinical study at the National Cancer Institute compared continuous intravenous 5-FU with IP 5-FU in patients undergoing surgical resections for carcinoma of the colon and at risk of tumor recurrence.[35] Although survival rates were not significantly different between the two groups, the total amount of 5-FU that was tolerated was significantly greater in the patients treated with IP 5-FU. Furthermore, the risk of local peritoneal cavity recurrence was significantly less in patients receiving IP therapy.

INTRAMUSCULAR INJECTION

The delivery of exact quantities of drug is usually assured by intramuscular (IM) administration, but the rate of drug absorption may vary widely. Factors that influence absorption rate include the vascularity of the injection site, the degree of ionization and lipid solubility of the drug, the volume of the injection, and the osmolality of the solution.[36]

The site of injection seems to be a particularly important determinant of the absorption rate of drugs after intramuscular administration. Drugs are usually injected into the arm (deltoid), thigh (vastus lateralis), or buttocks (gluteus maximus).

In one investigation, lidocaine plasma levels in patients with proven or suspected myocardial infarctions were determined after administration of 200 mg of the drug intramuscularly.[37] Injection sites were deltoid, lateral thigh, or buttocks. Injection into the deltoid muscle gave higher levels than injection into the lateral thigh, which in turn gave higher levels than injection into the buttocks. In a resting patient, the deltoid muscle has the greatest vascularity of the three sites studied. This may account for the more rapid absorption of lidocaine from this site. The generally low plasma levels obtained after injection into the buttocks may reflect the high affinity of lidocaine for fatty tissue and the poor vascularity of this tissue.

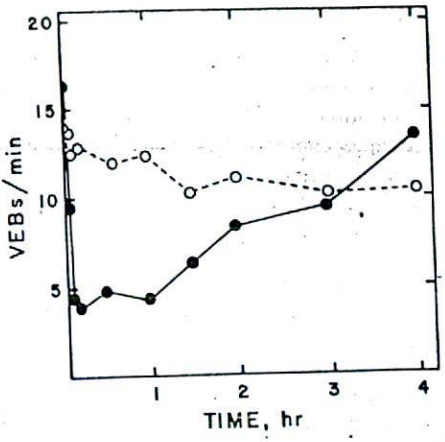

Fig. 6–1. Occurrence of ventricular ectopic beats (VEBs/min) after injection of lidocaine, 4.5 mg/kg, into the vastus lateralis (○) or the deltoid muscle (●). (Data from Schwartz, M.L., et al.[38])

Injection of 4.5 mg/kg lidocaine into the deltoid muscle of patients with ventricular ectopic beats (VEBs) has been found to give peak concentrations exceeding 2 μg/ml within 10 min. The rapid attainment of therapeutic blood levels is accompanied by a clinically significant reduction in VEBs. Considerably slower absorption and lower peak concentrations of lidocaine were found after injection into the vastus lateralis muscle. These lower levels did not produce a significant reduction in VEBs.[38] Clinical effect data are shown in Figure 6–1.

Intravenous lidocaine is widely used to prevent ventricular fibrillation among patients who are admitted to hospital during the early stages of acute myocardial infarction (MI). The real threat of ventricular fibrillation, however, is not after hospitalization but before admission—waiting for the ambulance or on the way to the hospital. Intervention by early administration of lidocaine by paramedics or others outside the hospital requires consideration

of intramuscular rather than intravenous administration.

To determine whether IM lidocaine before hospital admission is effective in preventing ventricular fibrillation, Koster and Dunning[39] undertook a controlled community study in the Netherlands. About 6000 patients with suspected MI were randomized to either a lidocaine group or a control group. Paramedics used an automatic injector to give a 400-mg dose of lidocaine into the patient's deltoid muscle. All subsequent events were documented by electrocardiographic (ECG) monitoring. The goal of the trial was to reduce the incidence of primary ventricular fibrillation in the 60-min period after lidocaine administration.

The diagnosis of acute MI was made in about one-third of the patients. Ventricular fibrillation occurring within 60 min after randomization was observed in 8 lidocaine-treated patients and in 17 control patients. A greater difference was observed during the 15 to 60 min period after injection. During this period 12 patients in the control group compared with only 2 in the lidocaine group developed ventricular fibrillation. The results suggest that early administration of lidocaine is useful but that patients have little protection from arrhythmias in the 15-min period after injection, perhaps related to slow absorption of the drug.

Initial evaluation of the hepatitis B vaccine under controlled conditions indicated a level of immunogenicity far higher than has been seen in actual use. This unexpectedly poor response may be related to the site of injection. For example, the combined seroconversion rate was 94% among 20 hemodialysis centers that vaccinated staff members in the arm but only 81% in 23 centers using buttock injection.[40] People who lack antibody to hepatitis B surface antigen after vaccination remain susceptible to hepatitis B infection.

In another investigation,[41] the standard three-injection series of hepatitis B vaccine given to 133 community hospital workers by buttock injection produced detectable levels of antibody in only 77 (58%). The next 50 workers to receive the vaccine were given the series of injections in the arm; antibody to hepatitis B surface antigen was found 1 month after the third dose in 87% of this group.

Ukena et al.[41] also gave a complete series of 3 doses by arm injection to 20 hospital workers who had not responded to the initial series given in the buttock; an antibody response was detected in 85% of them. The authors note that "this rate far exceeds the approximately 30 percent response rate among healthy persons revaccinated after nonresponse to arm injection." It is likely that the site of injection may influence the antibody response to hepatitis B vaccine and that healthy adults who do not respond to buttock injection have a good chance of responding when revaccinated in the arm.

Weber et al.[42] administered a series of 3 doses of hepatitis B plasma vaccine to 194 healthy hospital workers, largely female (88%) and relatively young (average age about 35 yr), by intramuscular buttock injection using a 1-inch, 23-gauge needle. Overall, only 56% of the subjects developed detectable antibody to hepatitis B surface antigen in serum after immunization. Logistic regression analysis revealed that the most important predictor for lack of antibody response to the vaccine was the weight-height index, computed as follows:

$$\text{WEIGHT-HEIGHT INDEX} = [\text{weight (kg)}]\,[\text{height (m)}]^{-p},$$

where p equals 2 for males and 1.5 for females. According to Weber et al., "the weight-height index is highly correlated with obesity as determined by skin-fold measurements and has been found to be the most satisfactory relative weight index."

Only 30% of employees with a weight-height index greater than the sex-adjusted 75th percentile for the US population developed significant post-immunization antibodies, compared with 63% of those employees under the 75th percentile. Inadvertent deposition of vaccine into fat may be responsible for the lower response rate following buttock injection.

Cockshott et al.[43] have estimated that buttock injection using a 3.5-cm needle results in deposition into fat rather than muscle in 85% of men and 95% of women. Undoubtedly, the problem is exacerbated in obese subjects and when a shorter needle is used.

Administration of human diploid-cell rabies vaccine in the gluteal area also results in lower neutralizing antibody titer than vaccination in the deltoid area.[44] In adults, the vaccine should always be given in the deltoid muscle; in children the anterolateral aspect of the thigh is also acceptable.

Serum levels and urinary excretion of cephacetrile, cephaloridine, and gentamicin were measured in healthy subjects after intramuscular injection

Table 6–1. Peak Cephradine Concentrations (μg/ml) in Plasma after Intramuscular Injections* at Different Sites to Male and Female Subjects†

Injection site	Males	Females
Gluteus maximus	11.1	4.3
Deltoid	11.7	10.2
Vastus lateralis	9.8	9.4

*Injected doses = 475 mg.
†Data from Vukovich, R.A. et al.[46]

into the thigh or buttocks.[45] Significantly faster absorption of cephacetrile was noted after injection into the thigh. Similar trends were apparent after injection of gentamicin and cephaloridine.

Male and female subjects each received a single intramuscular injection of cephradine, a cephalosporin antibiotic, once weekly for 3 consecutive weeks. The drug was injected into the gluteus maximus, vastus lateralis, or deltoid muscle.[46] Comparable cephradine concentrations in the serum were observed in males, irrespective of the injection site. Serum levels similar to those produced in males were observed in females after deltoid or vastus lateralis injection. Much lower levels, however, were found in females after injection into the gluteus maximus muscle; peak cephradine concentrations in the serum were less than half those observed after deltoid or vastus lateralis injection (Table 6–1). These findings provide an interesting example of sex differences in the intramuscular absorption of drugs.

Drugs are often given by intramuscular injection to patients who are unable to receive oral medication. This route is also used for drugs that are poorly absorbed from the gastrointestinal tract. Intramuscular injections are usually considered less hazardous and easier to administer than intravenous injections. On the other hand, they are often more painful. Intramuscular injections are routinely administered by nurses, other nonphysician medical personnel, or even by patients to themselves. The popularity of intramuscular injections is reflected in the results of a survey of more than 18,000 hospitalized patients monitored over a 10-yr period. More than half the patients received at least 1 intramuscular injection during their hospital stay.[47]

Many physicians assume that the intramuscular route is as reliable as the intravenous route and results in equal bioavailability of the injected drug. This is not always the case and there is now considerable evidence that intramuscular injection of drugs does not always assure rapid or complete absorption.

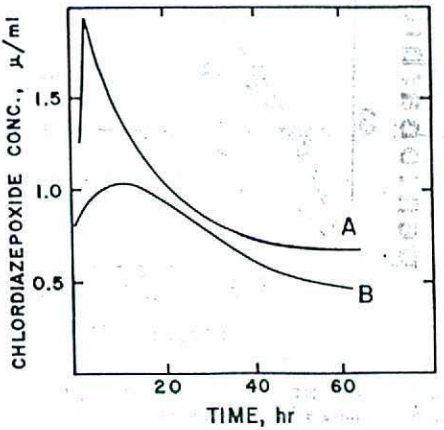

Fig. 6–2. Chlordiazepoxide concentrations in blood after oral (A) or intramuscular (B) administration of a 50-mg dose. (Data from Greenblatt, D.J., Shader, R.I., and Koch-Weser, J.[48])

Chlordiazepoxide is commonly given by intramuscular injection when rapid sedation is needed. However, some clinicians have observed that large doses of intramuscular chlordiazepoxide appear, at times, to be slowly effective or ineffective. Comparison of chlordiazepoxide concentrations in the blood after oral or intramuscular administration of 50-mg doses in healthy subjects indicates more rapid absorption after oral administration. On the average, peak concentrations of chlordiazepoxide were about 75% greater after the oral dose.[48] These data are shown in Figure 6–2. The time course of chlordiazepoxide concentration in blood in most subjects after intramuscular administration suggests that drug precipitates at the injection site.[49]

Similar results have been observed with pentobarbital.[50] Oral administration results in considerably higher pentobarbital levels in plasma than does intramuscular injection. This study also shows that giving the drug according to a specified injection technique (i.e., a defined needle size and site of injection) results in higher plasma levels than does routine, uncontrolled injections (Fig. 6–3).

There is little appreciation of the thickness of gluteal fat, particularly in female patients. Few female patients and less than 15% of male patients do in fact receive an intramuscular injection when a needle of the usual size is inserted into the but-

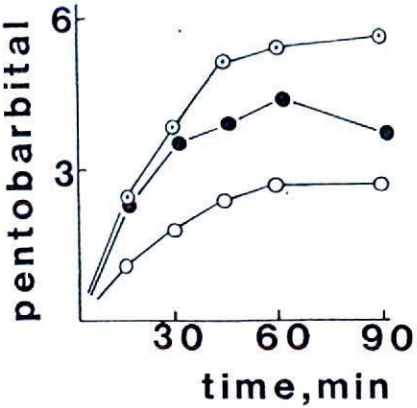

Fig. 6–3. Average pentobarbital concentrations (μg/ml) in plasma following a 100-mg dose. Key: (⊙) oral administration; (●) intramuscular injection, defined needle size and injection site; (○) intramuscular injection, unspecified. (Data from Nair, S.G., et al.[50])

tocks; most patients receive an intralipomatous injection.[43] If deposition into the muscle is desired, we need to choose needles whose length is appropriate for the site of injection and the patient's deposits of fat.

The use of intramuscular diazepam to provide rapid preanesthetic sedation and amnesia is also controversial. Several studies suggest that the absorption of diazepam after intramuscular injection is slow and erratic.[44–52] In contrast, diazepam absorption appears to be rapid, uniform, and complete after oral administration.

Clinical studies to evaluate diazepam as a pediatric premedication show that an oral dose with scopolamine provides satisfactory hypnosis and amnesia; intramuscular diazepam with the same dose of oral scopolamine is considerably less effective.[52] Studies in adults suggest that a 10 mg oral dose of diazepam fails to provide adequate sedation in only 12% of the patients whereas the same dose given intramuscularly shows a failure rate of 37%.[51,53]

Oral administration of thyroid hormone is satisfactory for most patients with hypothyroidism but there is some interest in an injection dosage form for patients with severe hypothyroidism complicated by other diseases, or for those in myxedematous coma. Unfortunately, studies in healthy adults indicate that intramuscular injection of triiodothyronine results in exceedingly slow absorption of the drug. Only 50% of the dose is absorbed 8 hr after injection. Absorption persists for more than 1 day after administration. It has been suggested that the medication be given intravenously if rapid onset of thyroid-hormone effect is desired.[55]

The slow absorption of some drugs after intramuscular administration is probably a result of precipitation at the injection site. The pH of phenytoin solution for injection is about 12; rapid precipitation is observed if the pH is adjusted to about 7. The dissolution of the crystalline precipitate of phenytoin in the muscle is slow, and absorption is unusually prolonged.

There is occasional need to switch from oral to intramuscular phenytoin because of medical or surgical emergencies. However, several studies have demonstrated that intramuscular administration of phenytoin in doses equal to previous oral doses results in a considerable decrease in plasma phenytoin levels and a potential loss of seizure control.[56,57] With the return to oral phenytoin, phenytoin concentrations in the plasma rise and attain levels significantly higher than steady-state levels before intramuscular therapy.[58] This transient "overshoot," which may last for several days, is the result of slow but continuous phenytoin absorption from the muscle depot during the re-initiation of oral therapy. The elevated phenytoin concentrations in the plasma during this period may be associated with adverse neurologic effects. A typical plasma phenytoin concentration versus time profile in epileptic patients during sequential oral, intramuscular, and oral dosing periods is shown in Figure 6-4.

A method for shifting from oral to intramuscular phenytoin administration in patients requiring parenteral therapy for as long as 2 wk has been proposed.[58] Based on the results of clinical studies, it has been recommended that the usual dose of phenytoin be increased by 50% when switching from oral to intramuscular administration. When a patient is switched back from intramuscular to oral therapy, a dose equal to one half of the original oral dose should be given for the same period of time the patient received intramuscular phenytoin. This dosing scheme seems to avoid significant changes in plasma phenytoin levels when switching from one route to the other.

Digoxin also precipitates at the injection site on intramuscular administration, resulting in slow and incomplete absorption as well as considerable local pain and tissue necrosis.[59] Although intramuscular

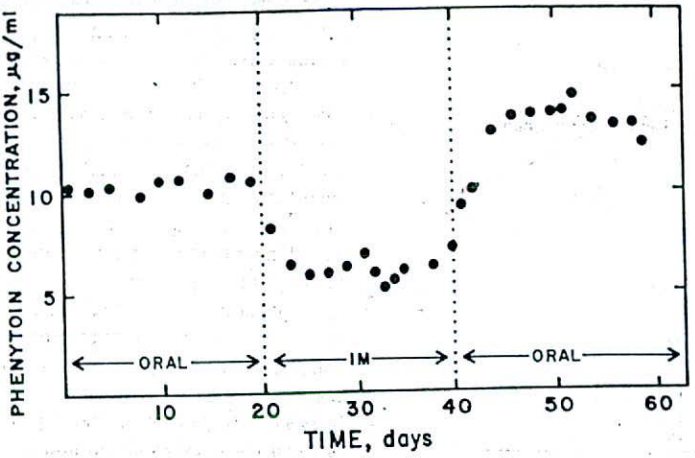

Fig. 6–4. Phenytoin levels in plasma during sequential oral, intramuscular, and oral dosing (4.7 mg/kg per day) in epileptic patients. (Data from Wilder, B.J., et al.[58])

digoxin produces adequate serum digoxin levels in some patients, it should be avoided.

Untoward local effects of intramuscular injections can be due to the mechanical aspects of the injection, or the properties of the drug or its solvent. Propylene glycol, a commonly used solvent, is a particular problem. These effects can develop immediately on injection or have a delayed onset. The release of creatine phosphokinase (CPK) from muscle cells into the blood is a common consequence of the trauma of intramuscular injections. Elevations in serum CPK tend to be greater when large volumes are injected, when the pH or tonicity of the injected solution is far from the physiologic range, or when the solution is intrinsically irritating.[60,61] Studies with intramuscular chlordiazepoxide indicate that the rise in CPK after injection is due largely to the solvent.[60]

Although local adverse effects of intramuscular injections are of concern for certain drugs, the overall incidence of clinically important local complications is low. Among some 26,000 hospitalized medical patients, 46% of whom received at least one intramuscular injection, local complications were reported in a total of only 48 patients (0.4% of all intramuscular recipients).[62] The most common adverse reactions were abscess formation at the injection site, local induration, erythema or wheal formation, and persistent pain. Injections of cephalothin and tetracycline presented the most frequent problems. Local complications were reported in 9 of the 83 patients (10.8%) receiving intramuscular cephalothin. The use of intramuscular injections of these high risk drugs needs to be reassessed.

There has been interest for some time in using the slow absorption of insoluble material in a muscle depot as a means of achieving prolonged drug effects. This aspect of parenteral therapy is considered in Chapter 7.

SUBCUTANEOUS INJECTION

Absorption of drugs from subcutaneous tissues is influenced by the same factors that determine the rate of absorption from intramuscular sites. Generally, it is held that the blood supply to this region is poorer than to muscle tissue and, consequently, drug absorption may be slower. Absorption may be hastened by massage, application of heat to increase blood flow to the injected area, local co-administration of vasodilators, or inclusion of the enzyme hyaluronidase in the drug solution. This enzyme breaks down the hyaluronic acid of the connective tissue matrix, allowing the drug solution to spread over a wider area. Absorption can be slowed by adding a vasoconstrictor such as epinephrine to the injection solution. This is commonly done to prolong the effects of local anesthetics.

The most important drug that is routinely administered subcutaneously is insulin. Studies in diabetic children show that with either subcutaneous or intramuscular injection, the absorption rate of insulin is about 50% faster when injected into the

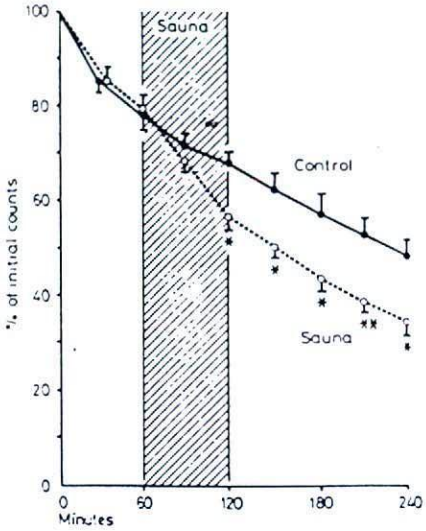

Fig. 6–5. Effect of sauna treatment on the disappearance of ^{125}I-insulin from subcutaneous injection site. (From Koivisto, V.A.[66])

arm rather than the thigh.[63] This difference could constitute a potential source of variability in diabetic control. These investigators also found that insulin injected either intramuscularly or subcutaneously is absorbed at about the same rate. This observation is contrary to the general impression that absorption from subcutaneous sites is slower than from intramuscular sites.

Studies in insulin-dependent diabetics show that exercise and local heating increase both adipose tissue blood flow and insulin absorption after a subcutaneous injection into the anterior thigh.[64] Local cooling decreased blood flow and insulin absorption. A strong correlation ($r = 0.97$) was observed between adipose tissue blood flow and the first-order absorption rate constant for insulin. These findings help explain why acute exercise in insulin-dependent diabetics is frequently associated with metabolic complications.[65] Studies in Finland indicate that sauna treatment can also accelerate insulin absorption (Fig. 6–5) and lead to hypoglycemia.[66] Such an effect might be prevented by taking a snack or reducing the insulin dose. Cigarette smoking causes peripheral vasoconstriction and may substantially reduce the rate of insulin absorption from subcutaneous tissues.

The duration of action of insulin after injection is controlled largely by its crystallinity. Insulin forms a poorly water-soluble complex when reacted with zinc chloride. Depending on the pH, it may precipitate either as an amorphous or a crystalline solid. Prompt Insulin Zinc Suspension (Semilente insulin) consists of amorphous insulin zinc complex. The drug is readily absorbed upon injection and has a relatively short duration of action (12 to 16 hr). Extended Insulin Zinc Suspension (Ultralente insulin) is made up predominantly of crystalline complex. It is slowly absorbed and has a longer duration of action (36 hr) than prompt insulin zinc suspension. Insulin Zinc Suspension (Lente insulin) is a mixture containing about 7 parts of crystalline to 3 parts of amorphous insulin zinc complex. It is intermediate in duration of action (24 to 28 hr). Another difference in the 3 formulations is their particle size. Prompt insulin consists of small particles; extended insulin is made up of relatively large particles.

EXTERNAL AND IMPLANTABLE PUMPS FOR CONTINUOUS PARENTERAL THERAPY

Until rather recently, the patient requiring continuous parenteral drug therapy had to be hospitalized and tethered to an intravenous drip system. The need to have more accurate delivery of various intravenous solutions and medications, however, has fostered the development of infusion pumps and regulators for bedside use in hospitalized patients to replace the traditional iv drip. Further developments in infusion pump technology, notably in the areas of electronic control and miniaturization, have now made continuous parenteral drug therapy available to ambulatory patients, thereby reducing costs, discomfort, and hospital time—and offering the promise of better treatment of disease.

There are several established portable infusion pumps that are intended to be worn externally. An example is the Auto Syringe (Travenol Labs, Chicago, IL), a battery-driven device that employs standard syringe reservoirs for drug delivery. Several models are available, weighing from 10 to 16 oz, and designed to hang vertically from a belt on the patient's hip. The device has an alarm system to indicate when the battery runs down or the catheter is plugged or kinked. Portable infusion pumps have been used largely for the continuous administration of insulin, but they may be useful for the delivery of antibiotics, cancer chemotherapeutic agents, and other drugs.

The Food and Drug Administration (FDA) has recently approved an implantable drug delivery

system (Infusaid; Infusaid Corp., Norwood, MA) for patients who require the continuous administration of heparin or cytotoxic agents. This disc-shaped device weighs about 200 g. It is usually implanted in a subcutaneous pocket in the upper chest or the lower abdominal wall and attached to a Silastic catheter surgically placed to deliver drug solution to a desired artery or vein. The pump consists of two chambers, separated by titanium bellows. The outer chamber contains a fluorocarbon that exerts a vapor pressure of several hundred millimeters of mercury at body temperature. This vapor pressure is the power source, compressing the bellows and forcing drug solution in the inner compartment into the catheter. Periodically, the drug chamber is refilled by percutaneous injection through a central injection port with a self-sealing septum. A side injection port is available on some models to permit bolus injections. The Infusaid pump can hold up to 50 ml of drug solution; flow rate may be varied, but must be factory-calibrated.

Insulin Administration

Patients with type I (insulin-dependent) diabetes mellitus, formerly called juvenile diabetes, do not respond to oral hypoglycemic agents and require exogenous insulin. Many forms of insulin are commercially available; they differ in concentration, time of onset, duration of action, purity, and source. The earliest use of regular insulin in patients with diabetes required at least four injections per day, associated with meals to reduce postprandial serum glucose concentrations. Today, combinations of slow- and intermediate-acting and regular insulin are used, and most patients require two injections daily, one before breakfast and the other before the evening meal. Although this regimen provides acceptable regulation in the majority of patients, all but the most fastidious in observing dietary restrictions and monitoring blood glucose for dosage adjustment will show large swings in serum glucose concentrations during the course of a day and average glucose concentrations well above normal limits.

Hyperglycemia may be a risk factor in the development of diabetic nephropathy, neuropathy, and retinopathy, and stricter control of blood glucose concentrations is now considered desirable to slow or prevent the progression of diabetic complications. The development of portable infusion pumps has been one element in this effort. Continuous administration of insulin in conjunction with glucose monitoring at home to adjust dosage is being widely investigated as a means of normalizing blood glucose in diabetic patients. These open-loop systems are typically designed to deliver insulin subcutaneously at a constant basal rate interrupted when necessary for before-meal bolus doses of regular insulin. Initial evaluation of this new approach to the treatment of diabetes is encouraging with respect to control of blood glucose, but more study is required to determine long-term benefits.

Mecklenburg et al.[67] compared the metabolic control achieved by glucose monitoring at home and the insulin-infusion pump with that previously obtained with conventional insulin therapy in a series of 100 patients with type I diabetes; the patients in the study were followed up for up to 15 months. The target range of capillary-blood glucose concentration was between 60 and 140 mg/dl. Fasting blood glucose decreased from a mean level of 201 mg/dl before insulin-pump therapy was begun to 158 mg/dl after 30 days, and to less than 140 mg/dl after 3 months on the pump. Statistically significant improvement in metabolic control was found in 71 of the 100 patients. Of the patients receiving insulin-pump therapy for at least 6 months, 62% had mean blood glucose values of 140 mg/dl or lower.

Similarly encouraging results have been observed by Rudolf et al.[68] in pregnant diabetic patients. An improvement in glucose control was achieved within the first month of treatment with the insulin pump and sustained to term. Prevention of maternal hyperglycemia may be important in minimizing the risks for the infant of the diabetic mother. Even modest elevations of maternal glucose levels during the third trimester of pregnancy have been associated with increased risk of perinatal mortality.

Continuous subcutaneous insulin infusion has resulted in improved glucose control in most insulin-dependent diabetics, but it has been much less successful in patients with brittle diabetes. This condition occurs in a small proportion of type I diabetics; it is characterized by unpredictable swings in blood glucose concentration, apparent changes in daily insulin requirement, and an increased number of hospital admissions for ketoacidosis or hypoglycemic coma. Poor glucose control in brittle diabetics may be related to irregular insulin absorption from subcutaneous tissue; therefore, these

patients may benefit from an alternative site of insulin administration.

Pickup et al.[69] found little improvement in metabolic control when brittle diabetics were switched from conventional insulin therapy to subcutaneous insulin-pump therapy. Significant improvements, however, were observed in 5 patients when insulin was infused continuously into the deltoid muscle rather than subcutaneously. One patient's disease could be controlled only by intravenous insulin.

The authors ascribe the poor effectiveness of subcutaneous insulin in these patients to erratic absorption. They note that factors such as variation in local subcutaneous blood flow and enzymatic destruction of insulin under the skin may contribute to the problem. Insulin absorption from muscle seems to be more predictable. Pickup et al., however, do not recommend continuous intramuscular insulin infusion as a routine outpatient treatment for brittle diabetes because of serious technical difficulties such as the insertion and long-term securing of the intramuscular cannula.

Pozza et al.[70] describe a patient with brittle diabetes in whom adequate metabolic control could not be achieved by continuous subcutaneous, intramuscular, or intravenous administration of insulin. Appreciable improvement in mean glucose concentration and mean amplitude of glycemia excursions was attained, however, by continuous intraperitoneal administration of insulin through a permanently inserted catheter. The authors suggest that "the intraperitoneal approach has the advantage of delivering insulin at a more physiological site, since the hormone reaches the liver before entering the peripheral circulation."

Infusion Pumps for Other Drugs

Outpatient treatment of severe congestive heart failure remains a problem because of the limited availability of orally effective inotropic agents. Berger and McSherry[71] have described a totally implantable infusion system (Infusaid) to administer dobutamine on an ambulatory basis to patients with refractory congestive heart failure.

Another Infusaid implantable pump has been approved by the FDA to deliver the aminoglycoside antibiotic amikacin directly to the site of infection in patients with osteomyelitis. Osteomyelitis infections are notoriously difficult to treat; severe cases may be incurable and require amputation. Pump treatment with targeted delivery may produce much higher antibiotic levels at the site of infection and thereby be more effective than conventional treatment. Furthermore, the device allows discharge of the patient from the hospital far earlier than the 8 to 10 wk period required to eradicate the infection because the patient receives continuous antibiotic treatment at home.

Both implantable and external infusion pumps have been used with success for the continuous delivery of heparin in the treatment of clotting disorders. Hattersley et al.[72] have described the use of continuous-pump heparin therapy in the treatment of patients with venous thrombosis or pulmonary embolism. The following protocol was used: *(a)* intravenous bolus of 50 units/kg heparin; *(b)* constant heparin infusion of 15 to 25 units/kg per hour; *(c)* modify infusion rate if necessary to maintain an activated coagulation time of 150 to 190 sec.

Efforts have also been directed to continuous-infusion cancer chemotherapy, through an arterial line for organ-specific treatment or through a venous line for systemic therapy; external, portable, and implanted pumps have been evaluated.[73] The rationale for arterial infusion to a specific organ is attainment of high drug concentration at the tumor site and reduced systemic exposure and toxicity. The basis for continuous venous administration is to overcome the short half-life of many cytotoxic drugs and ensure drug exposure to tumor cells during a growth phase.

Lokich et al.[74] described the use of subclavian vein catheterization and a portable infusion pump for continuous delivery of fluorouracil and other antineoplastic drugs to patients with metastatic malignancy. Phillips et al.[75] described the use of a totally implantable system for continuous intra-arterial delivery of antitumor drugs to 6 patients with malignant gliomas. The core of the system is an Infusaid pump, implanted in the infraclavicular subcutaneous pocket, that infused drug solution directly in the internal carotid artery. The Infusaid pump has also been used for direct delivery of antineoplastic drugs to the liver via the hepatic artery in patients with hepatic metastases.[73,76]

Gyves et al.[77] determined fluorouracil concentration in peritoneal fluid and plasma during a 5-day course of continuous intraperitoneal infusion of the drug at a dose of 1 g/day in 5 patients with colonic or gastric cancer. Drug administration involved an infusion pump connected to a peritoneal dialysis catheter implanted in the abdominal cavity and attached to an injection port.

Fluorouracil concentration in plasma ranged from 0.13 to 1.1 μM, whereas drug levels in peritoneal fluid ranged from 0.12 to 2.3 mM. This large difference in concentration was maintained over the 5-day period in each patient. The selective regional advantage of intraperitoneal infusion of fluorouracil, calculated from the ratio of steady-state concentration of drug in peritoneal fluid to that in plasma, ranged from 550 to 7852 in individual patients and averaged 2559.

Although the effectiveness of intraperitoneal infusion of antineoplastic drugs in the treatment of intraperitoneal and hepatic cancer remains to be demonstrated, the availability of implantable devices for convenient access to the peritoneal cavity and developments in infusion pump technology should facilitate further clinical investigation in this area.

Pain associated with advanced cancer is usually well controlled with oral medication. For those unable to take drugs by mouth, continuous subcutaneous infusion has become an established technique. Jones and Hanks[78] described a new portable infusion device that can be set to deliver opioid analgesics for more than 1 month.

INHALATION

The lungs are remarkably efficient organs for the transport of gases; the large surface area of the alveoli, the high permeability of the alveolar epithelium, and the rich blood supply perfusing the lungs facilitate rapid exchange between blood and inspired air. These characteristics are equally important for drug absorption and ensure the rapid uptake of drugs given by inhalation. An additional advantage of this route of administration is that the drug is not subject to first-pass hepatic metabolism; drug is absorbed directly into the bloodstream. Gaseous or volatile anesthetics are the most important examples of drugs routinely given by this route. Inhalation of amyl nitrate has been used in the past to abort attacks of angina. Nicotine, morphine, and tetrahydrocannibinol are rapidly absorbed following inhalation of tobacco, opium, or marijuana smoke.

There have been many investigations on the absorption of gases from the lungs, but relatively few concerning pulmonary absorption of drugs presented in the form of solid or liquid particulates. Useful information is available from a series of studies involving tracheal instillation of drug solutions in rats.[79] These studies indicate many similarities between gastrointestinal and pulmonary absorption. Most compounds seem to be absorbed by passive diffusion across a lipid-pore membrane. Large polar molecules like heparin are slowly absorbed.[80] Absorption of weak electrolytes like p-amino-salicylic acid, procainamide, or sulfisoxazole is a function of pH.[81] The absorption of lipid-soluble molecules is rapid.

Schanker et al.[82,83] compared the rates of pulmonary absorption of aerosolized *versus* intratracheally injected drug solutions in several animal species. At various times after drug administration, the lungs were removed and assayed for unabsorbed drug. The twelve drugs studied had widely different absorption rates. In the rat, after aerosol administration, absorption half-lives ranged from 0.3 min for antipyrine to 44 min for inulin. In all cases, however, the drug was absorbed approximately 2 times more rapidly when inhaled as an aerosol than when given by intratracheal instillation.

Therapeutic aerosols are usually produced by metered-dose inhalers, which provide unit doses of medication from fluorocarbon-pressurized canisters. An alternative approach involves continuously or intermittently generated wet aerosols from ultrasonic or jet nebulizers containing drug solutions; patients usually inhale the medication by tidal breathing.

Although, in principle, any drug intended for systemic effect may be given by way of the lungs, in practice, aerosol administration has been essentially limited to those drugs that affect pulmonary function. An exception is Medihaler Ergotamine, an aerosol device used to abort migraine and other vascular headaches. Aerosolized drugs used in the treatment of asthma and other reversible airflow obstructions include adrenocorticoid steroids (e.g., beclomethasone), bronchodilators (e.g., metaproterenol, albuterol), and antiallergics (e.g., cromolyn).[84]

One reason for the limited use of aerosols for inhalation is the relatively poor efficiency of the dosage form with respect to delivery of drug to the respiratory tract. A large fraction of an aerosolized dose impacts in the mouth and throat and is eventually swallowed rather than inhaled. Considerable variability may be observed in the amount of drug actually reaching the pulmonary tree. Therefore, despite the rapid absorption that can take place from the lungs, aerosol administration cannot be viewed as a routine alternative to intravenous in-

jection. Nevertheless, this route of administration is an important one for many drugs used in respiratory disorders.

At one time, there was controversy as to the best route of administration of bronchodilators. Inhaled bronchodilators are delivered directly to the target organ and minimize the risk of systemic effects. On the other hand, some argue for the intravenous route, particularly in the presence of increasing airways obstruction, because aerosol penetration is limited. The few comparative studies that have been carried out favor aerosol therapy. One study showed that intravenous and inhaled terbutaline provide equivalent benefit in chronic asthma, but that the inhalation route is preferred because it avoids systemic side effects.[85]

Pentamidine is one of few drugs effective in the prophylaxis and therapy of *Pneumocystis carinii* pneumonia (PCP) in patients with acquired immunodeficiency syndrome (AIDS), but the effectiveness of parenterally administered pentamidine is severely limited by serious side effects. Aerosolized pentamidine may be able to eradicate and prevent PCP without these adverse effects.

One report concerned the successful treatment of first episodes of PCP in 13 patients with AIDS by giving 600 mg of aerosolized pentamidine for 20 min daily for 21 days.[86] The only reported side effect was a cough in all but 1 patient.

The particle size of the aerosolized droplets or particulates, although difficult to control, is a critical factor in the efficacy of the dosage form. Large particles (20 μm) impact in the mouth, throat, and upper respiratory tract. Small particles (0.6 μm) penetrate more efficiently into the periphery of the pulmonary tree, from which absorption is most rapid, but total retention is poor and a large fraction of the dose is exhaled.

The condition of the patient may limit the penetration of aerosolized drug into the respiratory tract. The lack of effect of bronchodilator aerosols in severe asthma appears to be related to the patient's inability to inhale an adequate amount rather than to an intrinsic resistance to the drug.[87]

The development of the drug cromolyn and its aerosol dosage form has been particularly well documented. This compound is indicated for the prophylactic treatment of bronchial asthma; the drug is classified as an antiallergic, and is poorly absorbed from the gastrointestinal tract. After deposition in the lungs of various laboratory animals, the drug is well absorbed.[88] Studies in healthy subjects indicate about 5 to 10% of the administered dose is deposited in the lungs.[89] Poorer deposition has been observed in asthmatic patients.[90]

Cromolyn is administered by means of an inhalation device called a Spinhaler, designed to deliver the drug as a powder aerosol into the lungs when the device is actuated by the inspiratory effort. The drug for inhalation has a particle size range in which more than 50% by weight is between 2 and 6 μm.

The breath-actuated aerosol dosage form used for cromolyn may have some advantages over the conventional pressurized metered-dose inhaler; the conventional device requires synchronization of the release of the metered dose with the beginning of a deep inspiration to achieve good penetration of the lungs. This synchronization is not required for the breath-actuated device because release of the drug is automatically coordinated with the inspiratory phase of respiration.

A recent comparison of conventional versus breath-actuated aerosols of cromolyn in asthmatic children showed that the breath-actuated device was significantly more effective in reducing symptoms and bronchodilator intake.[91] Another clinical study compared the efficacy of isoproterenol from a breath-actuated inhaler and from a conventional inhaler.[92] The results indicated that both devices give an equally satisfactory degree of relief from bronchospasm, but there is a significant reduction in the number of doses of isoproterenol used during treatment with the breath-actuated device.

Unfortunately, the breath-actuated device is neither ideal nor suitable for all patients. Some patients are irritated by powder inhalation. The powder may be hygroscopic, making its use in humid conditions difficult. Some children are unable to inspire vigorously enough to activate the device.

A new powder inhaler, called a Turbuhaler, has been developed and is claimed to overcome most of the major problems associated with the Spinhaler.[93] It is described as a multidose system that is free of propellants, carriers, and other drug additives and that does not demand coordination between activation and inhalation.

There is convincing evidence that many patients who do not benefit from corticosteroid or bronchodilator aerosol therapy may fail to respond because they do not use the pressurized inhaler correctly. A report from the United Kingdom concerning treatment of asthmatic children with corticosteroid therapy concluded with the follow-

ing:[94] "Failure to respond to BDA (beclomethasone dipropionate aerosol) was frequently associated with low social status, crowded homes and the communication difficulties associated with immigrants to this country. It is likely that failure to inhale the corticosteroid aerosol properly and regularly is often responsible for a poor response." Another study found that 45 of 321 asthmatic patients used their inhalers incorrectly in spite of careful instruction. All but two of the patients who were unable to inhale correctly from a pressurized canister could use a breath-actuated device efficiently.[95]

Metered-dose inhalers (MDIs) are not easy to use, and patients usually receive little or no instruction in their use. Newman and Clarke[96] recommended that the patient "breathe out fully; hold both the head and the canister upright; place the mouthpieces between the lips; fire the inhaler while inhaling slowly and deeply; hold the breath for 10 seconds, or if less for as long as possible."

Lengthening the pathway between the actuator of the MDI and the mouth may reduce problems of coordination by introducing a delay between actuation and inhalation.[97] This idea is the basis for the development of spacers or cylinders that have a mouthpiece at one end and a fitting at the other to accommodate the mouthpiece of a conventional MDI. Spacers are claimed to reduce the need for optimal coordination and thereby to improve delivery of drugs to the lungs.

There is convincing evidence that spacers decrease oropharyngeal deposition of oral aerosols. As such, they may be particularly useful in reducing the topical side effects of inhaled corticosteroids. An inhalation aerosol formulation of triamcinolone acetonide with a spacer device is commercially available for treatment of asthma in children and adults; the product has been associated with a lower incidence of fungal colonization in the mouth.[98]

Evidence to support the use of spacers to improve the efficacy of bronchodilator aerosols is less convincing. Roughly, an equal number of studies have found a significant improvement when a spacer device was used and have failed to find an important difference. An example of a positive outcome is a study in children with exercise-induced asthma treated with placebo or terbutaline delivered by a conventional aerosol or an aerosol with a tube spacer.[99]

Both terbutaline treatments resulted in a significant increase in forced expiratory volume compared with placebo, but treatment with the device using a spacer produced significantly more improvement than did treatment with the conventional inhaler. The number of errors in inhalation technique was reduced when the spacer was used and this may account for the greater improvement.

Konig[97] concluded his review of MDI spacers as follows: "It seems that spacer devices are neither a breakthrough of such magnitude that their use should be made mandatory for users of MDIs nor a useless gimmick, but they definitely have a value somewhere between these extremes." Spacers may not improve the effects of aerosolized bronchodilator drugs in older children and adults with an adequate technique of inhalation, but may be useful in patients with problems of coordination and in young children. Spacers seem to be indicated in patients who develop oral candidiasis and other topical side effects during treatment with inhalation corticosteroids and in children unable to use the conventional MDI.

Nebulizers

A nebulizer makes an aerosol by blowing air or oxygen through a drug solution. Many inhaled drugs including albuterol, ipratropium, cromolyn sodium, and beclomethasone can be delivered in this way. Nebulization is effective because it allows high doses of drugs to be inhaled without any special effort to coordinate breathing. The aerosol is delivered through a face mask or a mouthpiece. Nebulized bronchodilators are particularly helpful in the acutely breathless patient both at home and in hospital. They can be used in young children and in patients on ventilators.[100]

Although the efficacy of nebulization is widely accepted, there are non-drug related complications associated with its use. Factors such as osmolality, acidity, preservatives, and bacterial contamination must be taken into consideration. Beasley et al.[101] suggest that nebulizer solutions be formulated as isotonic solutions with a pH > 5. Chemical preservatives should be avoided if possible. Solutions should be prepared under sterile conditions in unit dose vials, ready to use. Special attention must be paid to cleaning the nebulizer unit on a regular basis.

TOPICAL APPLICATION TO THE EYE

Drugs are administered to the eye for local effects such as miosis, mydriasis, anesthesia, or re-

duction of intraocular pressure. Steroids and anti-infective drugs are also frequently used in the eye.

Drugs may be applied in the form of sterile aqueous solutions, aqueous suspensions, solutions or suspensions in oil, ointments, or inserts intended to reside in the conjunctival cul-de-sac. After application, a drug penetrates the cornea, a barrier with both hydrophilic and lipophilic characteristics, to the aqueous humor bathing the lens. Penetration to the vitreous humor occurs through the ciliary bodies and iris.

The biphasic nature of the cornea suggests that the chemical form of a drug may influence the drug's penetration to the aqueous humor. This has been observed with dexamethasone.[104] In both the inflamed and uninflamed rabbit eye with intact corneal epithelium, the acetate derivative produced higher concentrations in the cornea and aqueous humor than did either the more polar phosphate derivative or the less polar free alcohol. The presence of intraocular inflammation increased the ability of the free alcohol to penetrate the cornea, but had little effect on the penetration of the acetate ester.

Based on the usual theories of drug absorption, one would expect the pH of the tear film to influence the ocular absorption of weak electrolytes. There is some evidence for this with pilocarpine, a cholinergic drug used in the treatment of glaucoma. Pilocarpine is a weak base (pKa 7.1); the drug is a more effective ocular hypotensive agent when administered at pH 6.5 (22% un-ionized) than at pH 5 (1% un-ionized).[105] The commercial preparation consists of an acid salt of pilocarpine buffered to about pH 4 to 5 for maximum chemical stability. Upon instillation of solutions of pilocarpine hydrochloride or nitrate in the eye, tear film pH is reduced by 1.1 to 1.6 pH units and remains below pretreatment pH for up to 1 hr.[106] These are not optimal conditions for the absorption of pilocarpine.

The pH-dependent ocular absorption of pilocarpine has been confirmed in more recent studies, but these investigators found a similar pH effect on the absorption of glycerin, a nonelectrolyte.[107] Sieg and Robinson concluded that although a pH-partition mechanism may play a small role, the overriding effect is pH-induced lacrimation. Over a pH range of 5 to 8, the lacrimation response decreases with increasing pH. Thus, at a higher pH less drug is washed away by nonspecific lacrimation, and bioavailability is improved. All drugs should show an improved absorption as pH is elevated within an acceptable range.

An important problem accompanying the instillation of eye drops is the immediate loss that occurs by drainage. The fraction of the drop lost increases as the instilled volume increases. Studies in the rabbit with pilocarpine show a marked dependence of miotic effect on drop size.[108] A 5-μl drop of pilocarpine produces about twice the peak intensity of effect and about 4 times the total miotic effect (determined from the area under the change in pupillary diameter versus time curve) as does a 75-μl drop containing the same amount of drug. A 5-fold decrease in volume from 25 to 5 μl, results in a 3-fold increase in fraction absorbed.[109]

Under normal conditions, the human eye can hold about 10 μl of fluid. The normal dropper used in commercial ophthalmic preparations delivers approximately 50 to 75 μl. The use of smaller drops (5 to 10 μl) of somewhat higher concentration would reduce costs and might higher concentration would reduce side effects. This suggestion is reinforced by the observation that instillation of 10 μl of a 2% epinephrine solution to rabbits gave the same pupillary response as did 50 μl of a 1% solution and produced less pain and lacrimation.[108]

Some patients are directed to instill more than 1 drop of an ophthalmic preparation at a time. Others require more than 1 preparation and administer them at the same time. The limited ability of the eye to accommodate fluid in excess of tear volume requires reconsideration of these practices because bioavailability and effectiveness may be compromised.[110] The change of pupillary diameter in the rabbit eye as a function of time after instillation of 25 μl of pilocarpine nitrate, followed by 25 μl of saline solution at various time intervals, is shown in Figure 6–6. The second drop reduces the activity of the first drop unless spaced about 5 min apart in rabbits and probably a slightly shorter time in man.[110] Rather than instilling 2 drops of a drug solution, it is advisable to raise the drug concentration and use a single smaller drop. There also appears to be a strong argument for a combination product, where possible, rather than separate solutions, when 2 or more drugs are required routinely for therapy.

It is generally believed that the inclusion of viscosity-increasing agents in an ophthalmic solution will increase ocular bioavailability by prolonging the contact time of drug in the eye. Studies in rabbits with pilocarpine in methylcellulose solu-

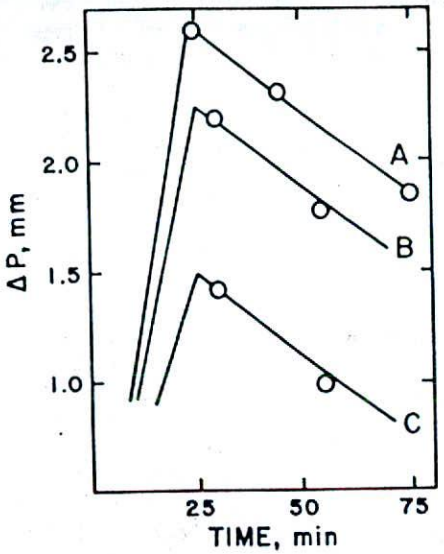

Fig. 6–6. Change in pupillary diameter (ΔP) after a 25-μl drop of pilocarpine (A) or the pilocarpine drop followed 2 min (B) or 30 sec (C) later by a drop of saline solution. (Data from Chrai, S.S., et al.[110])

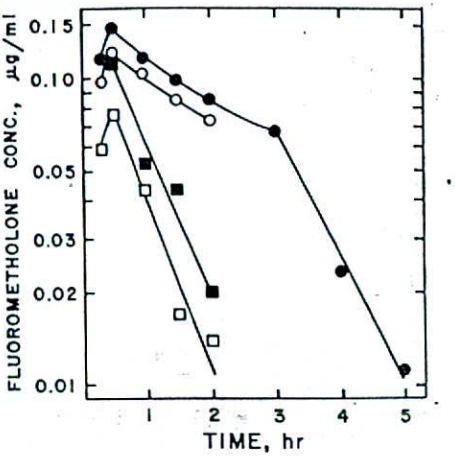

Fig. 6–7. Fluorometholone concentrations in aqueous humor after topical administration of 50 μl of a saturated solution (□), and 50 μl of a 0.01% (■), 0.05% (○), or 0.1% (●) suspension. (Data from Sieg, J.W., and Robinson, J.R.[112])

tions of different viscosity generally support this premise, but improvements in miotic activity were modest.[111] The investigators suggest that still smaller effects would be noted with smaller drops.

Studies with steroids have shown that the dosage form can have pronounced effects on drug concentrations in the eye. Steroid concentrations in the aqueous humor after topical application of fluorometholone suspensions and a saturated solution of the drug are shown in Figure 6–7. Peak concentrations occurred after 30 min, irrespective of the dosage form, but were higher after instillation of the suspensions than after administration of the saturated solution. The 0.1% and 0.05% suspensions produced a considerably longer effect compared to that observed with the more dilute suspension and the solution.[112]

Corneal and aqueous humor steroid concentrations resulting from topical application of 0.125% and 1.0% suspensions of prednisolone acetate have also been determined.[113] The 1.0% preparation produced much higher steroid levels at both sites in normal and inflamed rabbit eyes. These studies suggest that particles present in an ophthalmic suspension are retained within the cul-de-sac of the eye and once dissolved contribute significantly to the amount of steroid penetrating the cornea.

Many drugs are available in the form of sterile ophthalmic ointments. The major advantage of an ointment over an aqueous suspension or solution is the possibility of increased contact time and prolonged effect. The major disadvantage is the mixing problem between the ointment vehicle and the tears, which may limit the penetration rate. These characteristics of ophthalmic ointments are illustrated in the results of studies that determined steroid concentrations in the aqueous humor after application of a fluorometholone ointment to rabbit eye.[112] Peak concentrations were not reached until 3 hr after dosing, but drug levels persisted for far longer than observed after instillation of suspensions or a solution of the drug. The delay in attaining high drug levels may be overcome by instilling a drop of drug solution before applying the ointment.

Aqueous gels appear to have the same advantages as traditional oleaginous ophthalmic ointments. Much higher and more persistent levels of radioactivity were found in rabbit cornea and aqueous humor after administration of tritiated prednisolone acetate or tritiated prednisolone sodium phosphate in an aqueous gel than in the respective reference preparation, a suspension in the case of

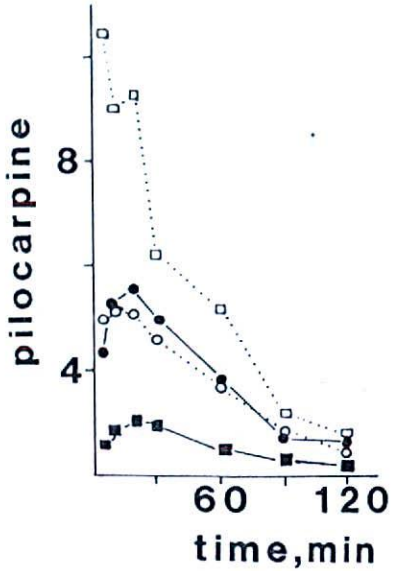

Fig. 6–8. Aqueous humor levels of pilocarpine (μg/ml) after topical dosing with 0.01 M ointment (●,○) or solution (■,□) in intact (●,■) or abraded (○,□) rabbit eyes. (Data from Sieg, J.W., and Robinson, J.R.[107])

the acetate and a solution in the case of the phosphate.[112]

Incorporation of pilocarpine into a petrolatum-based ointment vehicle resulted in increased drug levels in the aqueous humor of normal rabbit eyes compared to those produced by an equivalent dose of aqueous solution.[107] A different picture emerged when the rabbit's eyes were abraded. Abrasion markedly increased the bioavailability of pilocarpine from the aqueous solution, but had no effect on drug absorption from the ointment. The net result is that under these conditions bioavailability is greater from the solution than the ointment (Fig. 6–8).

The use of ophthalmic drug solutions or suspensions in oil has been limited, but there may be some advantage to this dosage form. One report noted that in healthy subjects pilocarpine dissolved in castor oil has a greater degree and duration of effect on the pupil than the same amount of drug given in aqueous solution.[115] Statistically significant drug effects were noted for as long as 24 hr after administration of the oil-based drops. Other approaches to prolonging the effects of drugs used in the eye are considered in Chapter 7.

Distinctions are rarely made in topical ophthalmic drug therapy between age groups. Generally, the same dose of an ophthalmic solution, suspension, or ointment is given to infants and adults. Recent experimental work challenges this lack of discrimination. Identical doses of 25 μl tritiated pilocarpine solution were instilled into the eyes of 20- and 60-day-old rabbits. Drug concentrations in the aqueous humor were always higher in the young rabbits. The total area under the drug concentration versus time curves differed by a factor of two.[116] These studies suggest that lower doses of eye medication may be appropriate in young children.

Despite the many problems that have been enumerated, topical application is an efficient way of delivering drug to various parts of the eye. This is seen clearly in a study on the ocular penetration of chloramphenicol.[117] Chloramphenicol concentrations were determined in the aqueous humor after administration of the drug as an ophthalmic ointment, subconjunctival injection, or intravenous injection. A 1% ointment produced peak chloramphenicol concentrations of 20 μg/ml; a 100 mg/kg intravenous dose of chloramphenicol resulted in peak levels of only 2 μg/ml. In all cases, the ointment was the most efficient means of drug delivery, providing the highest chloramphenicol concentration in the aqueous humor per mg of administered drug.

Although the eye is not a route for systemic drug administration, systemic absorption can occur. Systemic effects have been observed in laboratory animals after repetitive administration of certain eye drops, including those containing steroids. Systemic absorption probably results from entry of the drug into the lacrimal duct, which drains lacrimal fluid into the nasal cavity and ultimately into the gastrointestinal tract.

One study has shown that ordinary doses of phenylephrine eye drops significantly raised blood pressure in patients with insulin-dependent diabetes and in patients who had been taking reserpine or guanethidine.[118] Systolic and diastolic blood pressure rose by about 30 and 15 mm Hg, respectively, in these patients after 3 or 4 doses given over a 2-hr period before ocular surgery. There have been several reports of aplastic anemia in patients using chloramphenicol in eye drops or ophthalmic ointment.[119]

Finnish investigators measured atropine plasma levels and monitored blood pressure, heart rate, and salivary secretion in eight patients after application of 40 μl of 1% atropine ophthalmic solution

to the lower cul-de-sac of one eye in connection with ocular surgery.[120] Atropine plasma levels were determined by means of a sensitive radioreceptor assay.

An average peak plasma atropine concentration of 860 pg/ml was reached within 8 min in all patients. No effects on heart rate or blood pressure were observed when compared with placebo but 30 min after administration of atropine eye drops, salivary secretion was reduced.

The approval of timolol, a beta adrenergic antagonist, for the topical treatment of glaucoma has raised concerns over possible systemic absorption and adverse effects. Studies in the United States and Sweden indicate that routine use of timolol ophthalmic solution in healthy subjects results in detectable drug concentrations in blood and urine.[121,122] Small effects on exercise tachycardia were observed, but no effects on pulmonary function were noted. However, clinical reports of respiratory embarrassment and death in asthmatic patients taking ophthalmic timolol have prompted the United States Food and Drug Administration to contraindicate its use in such patients.[66] A review of the systemic side effects associated with the ophthalmic administration of timolol has been presented.[124] Caution should be used when ophthalmic timolol is given to elderly patients or those patients with contraindications to systemic beta-blockers, such as restrictive airway disease.

In 1986, two new beta-adrenergic-receptor blocking drugs, betaxolol and levobunolol, were approved by the US FDA for ophthalmic use in the treatment of chronic open-angle glaucoma. Betaxolol is a relatively selective beta blocker, blocking $beta_1$ receptors in the heart at concentrations below those required to block $beta_2$ receptors in the bronchi. At low doses, betaxolol is probably less likely to precipitate bronchospasm in patients with asthma than timolol or levobunolol.

As noted, drugs applied to the eye appear to be absorbed via the nasolacrimal duct, which drains lacrimal fluid into the nasal cavity, and ultimately into the GI tract. Zimmerman et al.[125] have evaluated two techniques to reduce nasolacrimal drainage and improve the therapeutic index of topically applied ophthalmic drugs: simple eyelid closure and nasolacrimal occlusion (NLO). Nasolacrimal occlusion involves pressing a fingertip to the inside corner of the eye after application of the medication.

Plasma concentrations of timolol were determined in healthy subjects 1 hr after instillation of 1 drop of 0.5% timolol maleate in the lower cul-de-sac of each eye, followed by NLO for 5 min, eyelid closure for 5 min, or no intervention. The same design was used to evaluate the penetration of topically applied fluorescein in the anterior chamber of the eye. Each person received 1 μl of 10% fluorescein in the lower cul-de-sac of each eye, and fluorophotometric readings were taken at intervals for up to 3 hr after administration.

Timolol concentration in plasma 1 hr after application of the drug to the eyes was about 1.3 ng/ml when there was no intervention and <0.5 ng/ml when eyelid closure or NLO was applied. On the other hand, relative fluorescein concentrations in the anterior chamber of the eye were significantly higher when eyelid closure or NLO followed administration of the marker.

The simple procedures of nasolacrimal occlusion or eyelid closure appear to reduce the systemic absorption of topical timolol. Furthermore, these procedures increase the concentration of fluorescein in the anterior chamber, presumably by increasing corneal contact time. Zimmerman et al.[125] suggest that "although only timolol and fluorescein were used in these experiments, theoretically, all topically applied drugs should manifest similar behavior. Generally, decreasing the amount of drug presented to the nasopharyngeal mucosa will decrease the systemic blood concentration of that drug. Similarly, prolonged corneal contact time will probably elevate intraocular concentration of a drug." These techniques may prove to be particularly useful in the treatment of asthmatic patients with ophthalmic beta blockers and in the treatment of hypertensive patients with ophthalmic epinephrine or phenylephrine where caution is required to avoid adverse effects.

INTRAVAGINAL APPLICATION

A large number of products are available for the intravaginal administration of various drugs in the form of tablets, creams, ointments, douches, and suppositories. Virtually all are intended to act locally in the treatment of bacterial or fungal infections or atrophic vaginitis, or to prevent conception.

Dinoprostone, the naturally occurring prostaglandin E_2, is available in the form of vaginal suppositories as a uterine stimulant to induce fetal abortion. This form of the drug also provides a safe and effective noninvasive method for inducing

labor. There is considerable interest in the development of long-acting intravaginal dosage forms of progestational agents or other contraceptive drugs. These dosage forms are considered in greater detail in Chapter 7. It is well recognized that drugs applied to the vagina may be absorbed, but there is little information available on specific drugs or on the biopharmaceutics of vaginal dosage forms.

The systemic absorption of metronidazole by the oral and vaginal routes was compared in healthy adult subjects.[126] Each subject received single 500-mg doses of metronidazole in the form of an oral, vaginal insert, or vaginal cream preparation on three occasions. Bioavailability from both vaginal products was about 20% compared with the oral preparation. Mean peak plasma concentrations were 15.6 μg/ml for the oral form and about 1.9 μg/ml for both the cream and the insert.

The data indicate that some vaginal absorption occurs from both the cream and insert preparations of metronidazole. These results underscore the concerns regarding the administration of vaginal metronidazole to pregnant patients. There are serious reservations as to the use of metronidazole in pregnancy; these reservations are not eliminated if the drug is given intravaginally.

INTRANASAL APPLICATION

Drugs are usually administered intranasally for the alleviation of local symptoms. These products typically contain decongestants, antihistamines, and corticosteroids. There is also interest in the intranasal route for the systemic administration of drugs. The nasal mucosa appears to be more permeable to drugs than the gastrointestinal mucosa, no local metabolism is known, and drugs absorbed through the nasal mucosa go directly to the blood stream and are not subject to first-pass hepatic metabolism.

The advantages of intranasal administration were demonstrated with propranolol, a drug subject to considerable presystemic metabolism and a low bioavailability after oral administration.[127] The time course of propranolol in serum and the total area under the serum level-time curve after intranasal administration of the drug in an aqueous gel were almost identical to those observed after intravenous administration, indicating rapid and complete absorption of therapeutic doses of propranolol after intranasal application. In contrast, the total area under the curve after oral administration was only 25% of that found after intravenous propranolol.

Nitroglycerin provides another example. Laryngoscopy and tracheal intubation produce increases in arterial pressure and heart rate that, in some patients, can provoke left ventricular failure, myocardial ischemia, and cerebral hemorrhage. Nitroglycerin (NTG) solution given intranasally before laryngoscopy and intubation can minimize these changes.[128]

Female patients undergoing breast surgery were randomized to either an NTG or control group. The NTG group received 2 ml of an NTG solution (60 mg), instilled intranasally 1 min before inducing anesthesia. The control group received no NTG. No change in arterial pressure was found in patients who received NTG before tracheal intubation. In the control group, an abrupt increase in arterial pressure (from 136 to 182 mm Hg) was observed immediately after intubation. NTG is rapidly absorbed when given intranasally; peak blood levels are reached within two minutes.[128] When NTG is given in this manner, it provides a safe, simple, and effective method to attenuate the hypertensive response to laryngoscopy and tracheal intubation.

Huang et al.,[129] using an in situ perfusion method in the rat, have determined that nasal absorption does not appear to be restricted to the nonionized form of the compound; the ionized species was absorbed about 25% as fast as the nonionized species. They also studied the effect of lipid solubility on the extent of nasal absorption using a small series of barbiturates, and found that absorption was dependent on the chloroform/water partition coefficient of the barbiturate.

The drug characteristics needed for good nasal absorption seem to be similar to those required for good absorption from the GI tract, but the membranes of the nasal mucosa appear to be more permeable than those of the gut. In general, peptides are not well absorbed after intranasal application but absorption can be promoted with certain additives such as surface-active agents. The nasal membranes may also be more sensitive than those of the gut; local toxicity may require attention for clinical application.

Some drugs have been found to affect the movement of nasal cilia. Cilia move in a well-organized and coordinated manner to propel the overlying mucus layer toward the back of the throat. In this way, inspired dust, allergens, and bacteria trapped

in the mucus are removed. Chronic ciliary stasis may lead to recurrent infection.

Hermens and Merkus[130] have reviewed the effects of drugs on nasal ciliary movement. They observed that "drugs in nasal preparations for local use as well as for systemic use, should not interfere with the self-cleaning capacity of the nose, effectuated by the ciliary epithelium. Many drugs and additives, however, have a negative effect on nasal ciliary function." Propranolol has a particularly profound effect on ciliary movement. Bile salts, widely evaluated as promoters of intranasal absorption, are also ciliotoxic. "The feasibility of nasal drug administration will depend in large part on the effects on the ciliated epithelium. These effects will determine the acceptability of the formulation by the patient and thus the success of long-term nasal drug delivery."

In an effort to better understand nasal absorption, particularly the effects of surfactants, Hersey and Jackson[131] described an *in vitro* model using nasal mucosa excised from dogs or rabbits to study permeability. The nasal mucosa was mounted as a flat sheet between two lucite half-chambers. Permeability was evaluated by measuring the unidirectional flux of several water-soluble compounds: water, sucrose, polyethylene glycol (mol wt 5000), and cholecystokinin octapeptide. In both these preparations, permeability coefficients decreased with increasing molecular weight.

The addition of 0.5% sodium deoxycholate to the mucosal bathing solution resulted in a threefold increase in permeability to sucrose. Similar increases in permeability were observed with cholecystokinin octapeptide. The increase in permeability was not reversible and was accompanied by histological evidence of extensive loss of the surface epithelial layer. These findings suggest that bile salts enhance nasal permeability by removing the epithelial cells, which constitute a major permeability barrier, and argue for extreme caution in using bile salts as adjuvants for intranasal administration of therapeutic agents.

Useful animal models to study nasal absorption have been developed. These models have been used to analyze the effect of molecular size and to elucidate structural requirements for absorption. Fisher et al.[132] measured nasal absorption in the rat of several radiolabeled water-soluble compounds ranging in molecular weight from about 200 to 70,000 daltons. The compounds were instilled into the nasal cavities of anesthetized animals and similar doses were given intravenously for comparison; serial samples of bile and urine were collected.

Nasal absorption of two organic acids (4-oxo-4H-1-benzopyran-2-carboxylic acid and p-aminohippuric acid) with molecular weights of about 200 daltons was complete or nearly complete; nasal absorption was about 15% for insulin (MW = 5,200), and 3% for dextran (MW = 70,000). An earlier study with the same methodology found that about 50% of a dose of sodium cromoglycate (MW = 512) was absorbed from the nasal cavity.

Applying these data, the investigators found a strong linear correlation between the log of the percentage of dose absorbed and the log of the molecular weight ($r = 0.996$). For these compounds, the proportion of an intranasal dose absorbed is largely a function of molecular weight, suggesting an aqueous channel mechanism for the absorption of water-soluble compounds.

McMartin et al.[133] used the same animal model to study the nasal absorption of an octapeptide (MW = 800) and a protein (horseradish peroxidase, MW = 30,000) and found bioavailabilities of 73% and 0.6% respectively. These findings were combined with published data for 23 other, mostly water-soluble compounds to examine the relationship between extent of absorption and molecular properties such as size, charge, or polarity.

The strongest correlation was with molecular weight. A log-log plot of nasal absorption versus molecular weight showed good bioavailability for all molecules up to about 1000 daltons molecular weight; the mean nasal absorption of the 15 compounds of MW <1000 was 70%. Absorption falls off sharply at higher molecular weights. A similar analysis of data on gastrointestinal absorption suggests a much lower molecular weight cutoff of about 200 daltons.

McMartin and his colleagues suggest that there are two mechanisms of drug transport from the nasal cavity. "A fast rate that is dependent on lipophilicity, and a slower rate that is dependent on molecular weight; the slower rate is nevertheless fast enough to give a high degree of absorption for low molecular weight polar compounds."

The first example of intranasal administration for systemic effects was the use of posterior pituitary hormones and related compounds such as oxytocin and desmopressin. Oxytocin (MW = 1007) is available as a nasal solution (40 units/ml) indicated to stimulate lactation. The usual dose is one spray

or three drops applied to one or both nostrils 2 to 3 min before nursing or pumping of breasts.

Desmopressin is a synthetic polypeptide (MW = 1183) structurally related to arginine vasopressin (antidiuretic hormone). Desmopressin acetate nasal solution (0.1 mg/ml) is indicated for the prevention or control of polydipsia, polyuria, and dehydration associated with diabetes insipidus caused by insufficient antidiuretic hormone.

Intranasal therapy has now been extended to anterior pituitary hormones, notably to luteinizing hormone-releasing hormone (LHRH) agonists, which, paradoxically, act pharmacologically as antagonists. These compounds are under investigation for the treatment of endometriosis and prostatic cancer. The best studied are leuprolide, buserelin, and nafarelin.

A randomized trial comparing buserelin with orchidectomy in patients with prostatic cancer concluded that the LHRH agonist was a safe and effective alternative to orchidectomy.[134] A randomized trial of subcutaneous leuprolide versus diethylstilbestrol (DES) in patients with prostate cancer and distant metastases found that leuprolide was "therapeutically equivalent to and causes fewer side effects than DES."[135]

More recently, Falkson and Vorobiof[136] reported on the efficacy, safety, and tolerability of daily intranasal administration of buserelin in the treatment of patients with metastatic prostatic cancer. Buserelin was used in the form of a nasal spray delivering 100 μg of drug per inhalation.

Twenty-five patients (80%) responded to treatment, 2 with complete remission, 12 with partial remission, and 11 who improved. The median baseline value for testosterone was 14.4 nmol/l, compared with values of 10.8 nmol/l after 1 month of treatment with buserelin.

Falkson and Vorobiof concluded that "intranasal buserelin is an effective, simple, and safe way to achieve androgen deprivation in the treatment of advanced prostatic cancer. This treatment neither causes the psychological problems of castration nor is it associated with the morbidity of estrogen administration." Furthermore, the nasal spray provides a method of administration that is more acceptable to patients than daily subcutaneous injections.

Intranasal administration of LHRH agonists has also been found to be effective in the treatment of endometriosis. Henzl et al.[137] randomized 213 patients with confirmed endometriosis to either nafarelin by nasal spray (400 or 800 μg/day) or oral danazol (800 mg/day) for 6 months of treatment. More than 80% of the patients in each treatment group had objective improvements as assessed by laparoscopy. The investigators concluded that nafarelin administration by nasal spray is an effective agent for treating endometriosis and has few side effects other than hypoestrogenism.

Do local inflammation and congestion associated with the common cold or hay fever modify the bioavailability of drugs administered intranasally? This interesting question was considered by Larsen et al.[138] who investigated the influence of experimental rhinitis on the intranasal absorption of buserelin, assessed by the gonadotropin response, in 24 healthy subjects. Each subject was treated with 200 μg buserelin in one nostril on each of two occasions. On one occasion, the drug was given 15 min after induction of inflammation by histamine; on the other occasion, the drug was given 15 min after saline solution treatment.

Treatment with histamine induced a significant increase in nasal airway resistance. After each dose of buserelin, serum luteinizing hormone (LH) concentrations rose steeply during the first 30 min after spraying, reaching a maximum at 3 to 4 hr followed by a gradual decline. The mean peak LH concentration was 17.7 mU/ml when the drug was preceded by saline and 19.8 mU/ml when buserelin followed pretreatment with histamine. The average AUC over 6 hours was 82 mU × hr/ml for the control arm and 84 mU × hr/ml for the experimental rhinitis arm. This study shows that the response to buserelin administered intranasally using a metered-dose pump spray was not affected by histamine-induced rhinitis.

The nasal absorption of other hormones such as insulin and calcitonin has also been studied. There is great interest in developing a dosage form of insulin that does not require injection. Intranasal administration results in measurable blood levels of insulin and a hypoglycemic response, but absorption is limited and not sufficiently reproducible. Nasal administration of insulin with a "promoter" such as bile salts improves bioavailability.

Aungst et al.[139] compared the absorption of insulin from different sites of application in adult male rats and also determined the effects of sodium glycocholate on absorption. Rectal insulin was more effective in lowering plasma glucose than was nasal, buccal, or sublingual insulin. The bioavailability of rectal insulin, after a dose of 10 U/kg

body weight, was estimated at about 20%, compared with a value of less than 1% for intranasal insulin.

Administration of insulin in a solution containing 5% sodium glycocholate increased absorption by each route of administration. Under these conditions, nasal and rectal insulin had similar bioavailability and were about half as effective as intramuscular insulin in reducing plasma glucose levels. Oral insulin at five times the dose (with or without bile salt) had no hypoglycemic effect.

Despite these promising studies in laboratory animals, a 5% solution of bile salt is clinically unacceptable. A more dilute and better tolerated preparation is unlikely to yield clinically adequate absorption of insulin. Most investigators have abandoned the notion that intranasal insulin could replace insulin injections. Interest persists, however, in combining intranasal insulin with injections to improve glycemic control in insulin-dependent diabetics and in supplementing drug therapy with intranasal insulin in non-insulin-dependent diabetic (NIDD) patients.

El-Etr et al.[140] reported on the efficacy of an insulin nasal spray administered before meals in eight NIDD patients. All hypoglycemic agents were stopped one week before testing. Insulin was administered as a calibrated spray twice in each nostril 20 min before a standardized lunch. Four sprays delivered a total dose of 1 U/kg body weight. The insulin solution contained 1% sodium deoxycholate as an absorption promoter. In the control study, insulin administration was omitted.

Plasma glucose increased from 12.7 mmol/l at baseline to 14.6 mmol/l, 1 hr after the standardized meal when no insulin was given. When intranasal insulin was administered, plasma glucose decreased from 12.3 mmol/l at baseline to 10.5 mmol/l, 1 hr after lunch. Differences in plasma glucose between drug and control studies persisted for up to 3 hr after the meal. The insulin level peaked at 10 min after insulin spray; the minimum glucose value was observed at 30 min after administration. The investigators concluded that "an insulin spray before lunch not only prevented the increase but also induced a decrease in the postprandial blood glucose in all patients tested without side-effects, apart from a slight nasal irritation for 1 to 2 minutes."

There is considerable interest in the use of calcitonin for the prevention or treatment of osteoporosis. Widespread use, however, will be impractical until a method of administration more suitable than subcutaneous injection can be developed. Addressing this point, Reginster et al.[141] evaluated the effectiveness of intranasal calcitonin in the prevention of early postmenopausal bone loss.

Seventy-nine women who had been menopausal for under 3 yr and who had not been specifically treated to prevent bone loss were randomized to a 12-month course of either calcium (500 mg/day) or calcium plus intranasal salmon calcitonin (50 IU/day). At the end of the study, bone mineral density had decreased in the calcium-only group by an average of 3.2% but had increased in the calcium plus calcitonin group by 1.4%. The decrease in bone mineral density in the calcium-only group confirms its lack of effectiveness in the prevention of osteoporosis. Intranasal salmon calcitonin, on the other hand, when given with calcium, appeared to counteract early postmenopausal bone loss.

APPLICATION TO THE SKIN

Dermatologic preparations are usually intended to act locally in the treatment of skin disorders. Application of drugs to the skin minimizes systemic exposure. This is exemplified by the safe and effective topical use of 5-fluorouracil to treat premalignant and malignant skin lesions. Systemic administration of 5-fluorouracil often results in serious adverse effects.

Systemic administration of glucocorticoids gives excellent results in clearing inflammatory skin lesions, but their adverse effects are considerable. Many of these diseases can be controlled by topical application of glucocorticoids with a dramatic decrease in the incidence of adverse effects. This advantage of topical drug therapy must be viewed as a relative rather than absolute one, because some systemic absorption occurs with almost all drugs.

Human skin consists of three distinct layers: the epidermis, the dermis, and the subcutaneous fat. The epidermis is the nonvascular, multilayered, outer region of the skin. The most superficial layer of the epidermis is the stratum corneum, which is composed of several layers of dead keratinized cells. The stratum corneum is generally recognized as the principal skin barrier to loss of water and to entry of foreign substances. The dermis or true skin is a highly vascular region. Drugs penetrating to this region are likely to reach the systemic circulation.

In principle, the vascularity of the dermis should produce a "sink" condition such that drug concentration is very much less than that present on the skin surface. Accordingly, further penetration of drug to tissues below the dermis is considered unlikely. Surprisingly, a review of the literature reveals several reports showing that deeper penetration can take place and that much higher subcutaneous drug levels can be achieved after topical application than after oral or parenteral administration.[142]

One study found that salicylate levels in the muscle adjacent to the site of topical application of labeled triethanolamine salicylate were 20 times higher than after oral administration of a dose of aspirin that produced blood levels 10 to 100 times greater than those after topical dosing. These results suggest that topical application of analgesics may provide relief of local pain and discomfort without systemic side effects.

The site of application and the state of the skin plays an important role in percutaneous absorption of drugs. Considerable regional variation in the percutaneous penetration of hydrocortisone has been observed in man.[143] Absorption is rapid in regions with large or numerous hair follicles. Hydrocortisone penetrates the scalp and forehead much more readily than it penetrates the ventral surface of the forearm. Absorption is decreased in some regions of skin having thickened stratum corneum (e.g., the foot). On the other hand, absorption from the palm, which has a fairly thick stratum corneum and no hair follicles, is comparable to that from the forearm. The scrotum provides almost no barrier to the absorption of hydrocortisone.

A more recent study examined the percutaneous absorption of sodium benzoate, caffeine, benzoic acid, and aspirin applied to different sites.[144] Skin permeability varied substantially, depending both on the properties of the drug and on the site of application. Whatever the compound applied, the forehead was about twice as permeable as the arm or abdomen. Application behind the ear produced intermediate results.

Cuts, diaper rash, inflammation, mild burns, or any other condition in which the stratum corneum is damaged or destroyed promotes the absorption of drugs through the skin.[145,146] Studies in patients with mycosis fungoides indicate that the percutaneous absorption of the antineoplastic drug carmustine through affected skin is much greater than through uninvolved skin.[147]

Stripping the skin with cellophane tape until it glistens removes the stratum corneum and causes damage to the upper layers of epidermis. This procedure is often used as a model for damaged and diseased skin. Stripped skin showed a fourfold increase in the penetration of hydrocortisone compared with intact skin.[148]

Hydration of the skin, by soaking in water or by occluding the skin surface with an impermeable material such as a plastic film, alters the barrier characteristics of the stratum corneum and promotes drug absorption. The enhancement of biologic activity of topical steroids by occlusion is well documented.[149] An occlusive dressing increases the absorption of hydrocortisone through normal human skin about tenfold.[146] The greatest percutaneous absorption of hydrocortisone was obtained by stripping the skin followed by a 24-hr occlusion. Penetration under these conditions was about 20 times the value for normal skin.[148] Occlusion also increases the percutaneous absorption of testosterone.[150] Certain lipophilic ointment bases may retard water loss from skin and promote hydration and drug absorption.

Aging and environmental factors that lead to dehydration of the skin can retard drug absorption. Environmental temperature can affect the hydration of the stratum corneum as well as the local blood flow. The absorption of a topically applied cholinesterase inhibitor from the cheek in normal male subjects increased 8-fold when the subjects were exposed to increasing temperatures ranging from $-18°C$ to $46°C$.[151]

The chemical form of the drug and the vehicle in which the drug is incorporated can have an important influence on percutaneous absorption.[152] For example, the efficacy of fluocinolone acetonide in inflammatory dermatoses (eczema and psoriasis) strongly depends on the vehicle.[153] An ointment formulation of 0.025% fluocinolone acetonide dissolved in propylene glycol and dispersed in soft paraffin was compared with 0.025% microcrystalline drug suspended in soft paraffin. The preparation containing drug dissolved, rather than suspended, in the ointment was significantly more effective in both eczema and psoriasis patients.

A human bioassay system was used to compare formulations of topically applied corticosteroids.[154] The test is based on the local vasoconstriction and skin blanching produced by penetration of the steroid through the stratum corneum. The degree of blanching is used as an index of bioavailability.

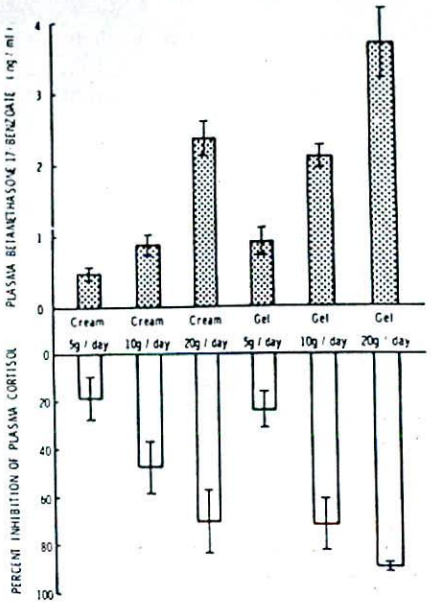

Fig. 6–9. Average levels of betamethasone 17-benzoate in plasma and inhibition of plasma cortisol after repeated applications of a cream or a gel base. (From Mizuchi, A., et al.[156] Copyright 1969, Baltimore, Williams & Wilkins.)

Examples of large differences between products containing the same amount of drug were common. In another study, using the same methodology, a proprietary cream containing 0.1% hydrocortisone was found to be substantially more effective than several other commercial formulations containing 1% hydrocortisone.[155]

The percutaneous absorption of betamethasone 17-benzoate has been studied in patients with skin disorders following application of either a gel or a cream.[156] Betamethasone concentrations in plasma and inhibition of plasma cortisol were significantly greater following the use of the gel rather than the cream (Fig. 6–9). The results of these studies and others convincingly demonstrate that dermatologic products are not necessarily therapeutically interchangeable.

The incorporation of certain chemicals such as dimethyl sulfoxide (DMSO) into topical formulations has been advocated to enhance penetration. In vitro and in vivo studies suggest that DMSO enhances the percutaneous absorption of many drugs, possibly by producing structural changes in the skin, such as swelling of the stratum corneum, and possibly by replacement of water as the continuous membrane phase of the skin barrier.[157] The use of DMSO in dermatologic products, however, remains controversial; questions of both safety and efficacy persist.

Other agents have also been studied as potential "penetration enhancers." One report presents the results of the vasoconstrictor assay following application of betamethasone 17-benzoate with different enhancing agents.[158] Propylene glycol with oleic acid, propylene glycol with azone, and dimethylformamide, among other agents, increased steroid bioavailability. The investigators caution, however, that irritant effects may make some penetration enhancers unacceptable for clinical use.

Despite the importance of biopharmaceutics in the development of drug products intended to be applied to the skin, surprising little work has been carried out to quantitatively define dose-response relationships. An important exception is the work of Wester and Maibach.[159] Carbon-14 labeled testosterone, hydrocortisone, and benzoic acid in organic solvent were applied to a uniform area of skin of human male subjects; absorption was estimated by measuring urinary excretion of total ^{14}C. With testosterone, concentration was increased from 3 to 400 $\mu g/cm^2$ in 3 steps. Although the total amount absorbed increased with dose, the percent absorbed decreased from 11.8 to 2.8%. Similar decreases in the efficiency of percutaneous absorption with increasing drug concentration were observed with hydrocortisone and benzoic acid. The data are summarized in Table 6–2. The reason for this dose-dependency is not clear; whether or not it will be observed with more complex formulations of drug remains to be determined.

These investigators used a similar approach in monkeys to determine if the percutaneous absorption of hydrocortisone changes with repeated applications.[160] Radiolabeled hydrocortisone was applied to the forearm on day 1, followed by 7 days of application of nonradioactive drug. On day 8, the labeled drug was again applied. The absorption of hydrocortisone increased considerably during repeated administration, whether it was applied in an acetone vehicle or an emulsion ointment base. About 0.5% of the applied dose was absorbed after the first dose of ointment. This increased to about 2% after the last dose (Fig. 6–10). Long-term application of hydrocortisone may alter the percutaneous barrier, resulting in enhanced penetration. Similar results have been observed with salicylic

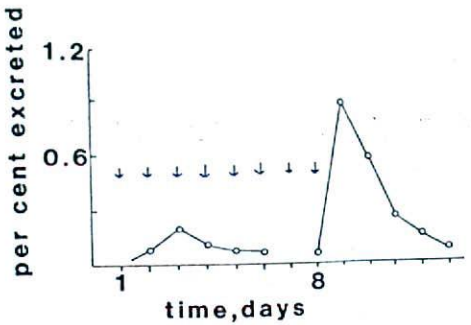

Fig. 6–10. Percutaneous absorption of ^{14}C-hydrocortisone (estimated from urinary excretion data) on day 1 and day 8; nonradioactive drug was applied on days 2 through 7. The ointment containing hydrocortisone was applied to the same site each day. (Data from Wester, R.C., Noonan, P.K., and Maibach, H.I.[160])

acid,[161] but these findings are less surprising because of the keratolytic effects of the drug.

The unexpected results following repeated application of hydrocortisone in monkeys were not reproduced in a more recent study in human subjects that compared the penetration of hydrocortisone, testosterone, and estradiol following repeated administration with that observed after a single dose.[162] The drugs were applied to the ventral forearm skin once a day for 14 days. The first and eighth dose were radiolabeled.

The mean % dose absorbed for testosterone and estradiol were nearly the same for both test doses. Urinary excretion of labeled hydrocortisone was about 30% greater following the eighth dose than after the first dose, but the difference was not statistically significant. More work is needed because many questions pertaining to the effect of repeated application on percutaneous absorption in humans remain unanswered.

Measuring radioactivity in urine following topical application of a labeled compound is a standard method for determining percutaneous absorption.[148] In an attempt to find an easier way to assess absorption after topical administration, Rougier et al.[144] compared urinary excretion of radioactivity following topical application of labeled sodium benzoate, caffeine, benzoic acid, or aspirin, to four different sites, with the amount of radioactivity in the stratum corneum at these sites shortly after administration.

Subjects were studied on two different occasions. The first study involved urinary excretion of labeled drug and the second concerned skin penetration. Thirty minutes after the second application, and after washing, the stratum corneum of the treated area was removed by 15 successive strippings with cellophane tape and the radioactivity contained therein was measured.

A strong linear correlation was observed between the amount of drug present in the stratum corneum shortly after application and urinary excretion of radioactivity. The investigators concluded that the stripping method can be used to make predictions of percutaneous absorption of different agents, irrespective of site of application, by measuring the quantity present in the stratum corneum after application. For many drugs it may be possible to carry out this determination with unlabeled compound because of the relatively high drug concentration in the stratum corneum.

In vitro techniques to estimate percutaneous absorption usually involve placing a piece of excised skin in a diffusion chamber, applying radioactive compound to one side of the skin, and then assaying for radioactivity in the collection vessel on the other side. Excised human cadaver skin and animal skin have been used; the skin may be intact or separated into epidermis or dermis. These methods are probably of value to the extent that they distinguish compounds with low permeability from those with high permeability.

Live animal models have also been used to study percutaneous absorption. In general, percutaneous absorption in the pig, rhesus monkey, and squirrel monkey is usually similar to that in man, whereas in the rat and rabbit skin penetration is greater than that observed in man.[148]

The idea of bioavailability as applied to drugs that are intended to act locally in the skin is a

Table 6–2. Percutaneous Absorption of Different Doses of Hydrocortisone and Benzoic Acid in Man*

	Hydrocortisone (μg/cm²)		Benzoic acid (μg/cm²)		
	4	40	3	400	2000
Amount absorbed (μg)	0.06	0.24	1.1	102.8	288
% Absorbed	1.6	0.6	37	25.7	14.4

*Data from Wester, R.C., and Maibach, H.I.[159]

confusing one. We wish to have maximum penetration of the drug into the skin; yet, we wish to minimize systemic absorption, to avoid adverse effects. Unfortunately, this delicate balance is not always achieved. Life-threatening systemic toxicity has been observed following liberal application of boric acid preparations to damaged skin of human infants. Substantial absorption, high blood levels, and clinical toxicity requiring forced diuresis were observed in a patient using a 12% salicylic acid ointment applied to 85 to 90% of the body surface for treatment of hyperkeratosis.[162]

Hexachlorophene bathing of infants had been widely advocated as effective prophylaxis against nursery epidemics of staphylococcal skin infections. However, clinical studies in newborn infants bathed daily with 3% hexachlorophene lotion showing measurable blood levels of the drug (as high as 0.6 μg/ml)[164] and toxicologic studies in newborn monkeys bathed for 90 days with this product showing blood levels of about 2 μg/ml and brain lesions,[165] have challenged the safety of this practice. A more recent paper reported that of 18 children with normal skin, accidentally intoxicated by a talc powder containing 6% hexachlorophene, 4 died and 2 remained paraplegic.[166]

Systemic toxicity of topically applied drugs is of particular concern in infants because they appear to absorb drugs through the skin as efficiently as do adults and the ratio of surface area to body weight in the newborn is 3 times that in adults.[150] The same strength formulation applied to the same relative area may result in much higher blood levels of drug in the infant than in the adult.

Although hexachlorophene is no longer used in over-the-counter products in the United States, it continues to be used by surgical staffs in hospitals. An important study in Sweden has revealed that among 460 children born to nurses who had been using soap containing 1 to 3% hexachlorophene, 25 had severe congenital defects, 3 had Down's syndrome, and another 46 had minor deformities.[167] These figures represent a birth defect rate 5 times that expected in the general population. The National Institute of Child Health and Human Development has recommended that women working in hospitals not use hexachlorophene-containing products.

Another drug that has had extensive use in dermatologic products but is now under scrutiny is gamma benzene hexachloride (lindane).[160] This compound is effective for the treatment of scabies and lice (pediculosis). Experimental studies have demonstrated that gamma benzene hexachloride can be absorbed from the skin and convulsions and death occur in animals after topical application of large amounts of the drug. Convulsions have also been reported in children after excessive topical application of commercial products. The Medical Letter on Drugs and Therapeutics cautions against prolonged or excessive use and suggests that alternative therapy such as sulfur in petrolatum may be safer for infants and children.[168]

Preparations designed to be applied to the skin to repel insects have been widely used for many years. The most effective topical insect repellent known is diethyltoluamide, commonly called "deet." Deet is absorbed through the skin into the systemic circulation and has caused serious toxic effects in children and adults, especially when used in high concentrations. Prolonged or excessive application of any insect repellent should be avoided.[169]

Although topical steroids are far safer in treating skin disease than systemically administered steroids, percutaneous absorption may lead to suppression of pituitary ACTH production and to reduced cortisol production by the adrenal cortex. The degree to which this occurs depends on the potency of the steroid, the amount used, the area of skin to which it is applied, the duration of treatment, and the amount of occlusion.

As a general rule, little effect on cortisol production is likely to occur with up to 50 g weekly for an adult or 15 g weekly for a child of a potent steroid ointment used without occlusion.[170] Frequent repeat prescriptions of potent topical steroids should be dispensed only after re-examination and consideration of possible alternative treatments.

A 2% topical formulation of minoxidil, a potent vasodilator used in severe hypertension, is now available for treatment of male pattern baldness. Franz[171] has estimated that 2 to 4% of a dose applied to the scalp is absorbed. Based on these findings, application of a 2% lotion twice a day to the entire scalp may provide a systemic dose of about 2 mg/day. This is less than the recommended oral adult antihypertensive dose of 10 to 40 mg/day. Short-term use of minoxidil has resulted in minimal decreases in blood pressure in normotensive patients; whether topical minoxidil has a hypotensive effect on patients with hypertension is not clear.[172]

There is now considerable interest in the topical application of drugs intended for systemic effects.

This route of administration may be useful for drugs with low bioavailability after oral administration due to first-pass metabolism. It may be particularly useful for short-acting drugs since percutaneous absorption tends to be slow, and prolonged effects may be realized. Most attention has been given to topical preparations of nitroglycerin, a compound with low oral bioavailability and a short duration of action, but one that remains important in the prevention and treatment of angina pectoris.

Nitroglycerin ointment has been available for more than 20 years, but only recently has its advantage been realized. Comparative studies of the effects of nitroglycerin ointment and placebo in 14 patients with angina pectoris have shown that nitroglycerin ointment produces a significant increase in exercise capacity, which persists for at least 3 hr.[173] The effects of the ointment are comparable to those produced by sublingual nitroglycerin, but of far longer duration. The effects of buccal nitroglycerin are usually dissipated in 30 min or less. Other studies have confirmed and extended these findings.[174-176] The ointment, however, has a slower onset of action than buccal medication and is never used for acute angina.

Nitroglycerin ointment is available in a 2% strength in a lanolin-petrolatum base. Each inch squeezed from the tube contains 15 mg nitroglycerin. The patient is titrated in 1/2-in. increments until a satisfactory dose is found. The ointment is usually applied every 4 to 6 hr to the anterior chest and covered with an occlusive wrap fixed with adhesive. The amount of nitroglycerin absorbed after topical application is a function of both the dose and the surface area over which it is applied.[177] Applying twice the dose (32 mg vs 16 mg) over a fixed area of skin resulted in almost twice the area under the nitroglycerin concentration in blood versus time curve for a 90-min period following administration. Increasing the skin surface area over which a fixed dose (16 mg) of nitroglycerin ointment is applied by a factor of 4, results in a 2-fold increase in the area under the curve.

Other lipid-soluble potent drugs may also yield clinically useful blood levels after topical application to the skin. A hydroalcoholic gel containing estradiol 0.6 mg/g, applied on the lower part of the abdomen, was used for cyclic (3 weeks on, 1 week off) replacement therapy in postmenopausal women. Increased serum concentrations of estradiol and estrone were observed during six months of treatment. Therapy was effective in abolishing hot flushes in most women.[178]

Lichen sclerosus, a chronic cutaneous disorder that most commonly occurs on the vulva in postmenopausal women and that is characterized by decreased levels of dihydrotestosterone, free testosterone, and androstenedione, was treated with topical testosterone.[179] All patients were given 2% testosterone propionate in white petrolatum for application to the vulva twice a day. After several months of treatment, dihydrotestosterone and testosterone levels rose and exceeded normal values. This was accompanied by clinical improvement in most cases.

Prolonged-release dosage forms of drugs intended to be applied to the skin for systemic effects are considered in Chapter 7.

BUCCAL OR SUBLINGUAL ADMINISTRATION

Certain tablets are intended to be placed beneath the tongue or in the cheek pouch and retained in the mouth. These regions are vascular and allow rapid absorption of certain drugs in a manner consistent with pH-partition theory. The buccal or sublingual route appears ideal for lipid-soluble drugs that are metabolized in the gastrointestinal tract or liver during absorption, because the blood supply draining the buccal cavity empties directly into the systemic circulation and bypasses the liver. In general, buccal or sublingual tablets are designed to disintegrate and dissolve slowly in the mouth to minimize the possibility of swallowing part of the dose. Exceptions include nitroglycerin and isosorbide dinitrate, which should dissolve within seconds to provide prompt relief for acute anginal episodes.

This mode of therapy is most frequently used for the administration of nitrates and certain hormones such as methyltestosterone, testosterone, and oxytocin, but buccal absorption of many drugs including estradiol, sympathomimetic amines, methadone, meperidine, buprenorphine, lidocaine, chlorpheniramine, imipramine, desipramine, and barbiturates has been demonstrated.[180-184] The pH of saliva is usually about 6. Increasing the pH of fluids in the buccal cavity promotes the absorption of weak bases but reduces the absorption of weak acids.[180-182]

The buccal absorption of flurbiprofen, a nonsteroidal anti-inflammatory drug, was studied in human subjects by delivering a solution of the drug

buffered to pH 5.5 or 7.0 through a flow cell in contact with the buccal membrane of the mouth.[185] Flurbiprofen is a weak acid. Consequently, absorption was greater at pH 5.5 where the acid was less dissociated than at pH 7.0. The investigators concluded that the buccal membrane was essentially lipoidal, showing no evidence of aqueous pores.

Although similarities exist between gastrointestinal and buccal absorption of drugs, some important differences must also exist. Clindamycin, which is known to be well absorbed from the gastrointestinal tract, is absorbed poorly, if at all, from the buccal cavity over the pH range of 4.0 to 8.5.[186] A higher degree of lipid solubility may be required for good absorption from the buccal cavity than from the gastrointestinal tract.

Other differences between buccal and gastrointestinal absorption have been identified in recent studies with β-blockers.[187,188] At least for some drugs, loss of drug from the oral cavity is not synonymous with systemic absorption; a storage compartment in the buccal membrane appears to exist. Once a drug is in the storage compartment, it may repartition into the oral cavity or be slowly absorbed into the systemic circulation. This phenomenon may be responsible for the slow absorption of buprenorphine after buccal administration.[184] A 2-fold difference between loss of drug from the oral cavity and appearance of drug in the systemic circulation has been observed with morphine.[189] At pH 6.5, 82% of a dose of morphine sulfate was recovered from the mouth after a 10-min exposure, suggesting that 18% of the dose was absorbed. A second study comparing the total area under the morphine concentration in plasma versus time curve after buccal and intramuscular administration indicated that the relative bioavailability of morphine from the oral cavity was only 9%.

Sublingual nitroglycerin remains the treatment of choice in the acute management of angina pectoris. Its advantages are thought to include a lack of tolerance, ease of administration, and rapid, consistent, and almost complete absorption. Some of these ideas have been challenged by recent studies.[190] Sublingual nitroglycerin tablets (0.4 mg) were given to healthy subjects and blood samples were collected for 3 hours to determine nitroglycerin levels. The tablet was placed under the subject's tongue and moistened with water; all subjects were asked to maintain the tablet in place and to avoid swallowing. After 8 min, they were instructed to spit out the remains of the tablets; the mouth was then rinsed with water and the rinsings added to the first collection. This material was assayed for residual nitroglycerin. All subjects also received intravenous nitroglycerin, so absolute bioavailability could be calculated.

Nitroglycerin levels were variable after sublingual administration. Bioavailability ranged from 3 to 113%, with an average value of about 40%. The mean time to peak concentration was about 5 min but in some subjects the peak was not observed until 10 min after administration. On the average, about 30% of the dose was recovered from the mouth rinsings taken at 8 min after administration. The rest of the dose presumably was swallowed and metabolized in the GI tract and liver.

The low and variable absorption of sublingual nitroglycerin may be related to the patient's inability to maintain the dose in the mouth without swallowing and to inadequate moisture in the mouth. A dry mouth has been cited as a factor in patients who appear resistant to nitroglycerin. Dry mucous membranes in patients experiencing anginal pain are expected. One investigator proposed that it should be routine practice to ensure that the sublingual mucosa is sufficiently moist to facilitate the dissolution of sublingual tablets of nitroglycerin.[191]

Nicotine gum was developed as substitution therapy to help people stop smoking. The preparation consists of nicotine bound to an ion exchange resin and incorporated into a gum base. The resin is expected to release almost all its nicotine over 20 to 30 min of chewing. The gum also contains a bicarbonate buffer to enhance the buccal absorption of nicotine.

Nicotine levels in the blood were compared after cigarette smoking and chewing nicotine gum.[192] In the first phase of the study, subjects abstained from cigarette smoking and chewed gum containing either 2- or 4-mg nicotine every hour from 9 AM to 8 PM. Subjects were asked to chew the gum slowly and steadily for 20 min. In the next phase of the study, subjects smoked cigarettes without restriction and without the use of gum. An average of nearly two packs of cigarettes per day were consumed.

The cigarettes provided a total of about 34 mg nicotine per day and steady-state concentrations in blood of 25 to 30 ng/ml nicotine. Average blood nicotine concentrations for subjects chewing 2- and 4-mg gum were only 29% and 42%, respectively,

of that observed while smoking cigarettes. Complete delivery of nicotine in the gum would have provided a daily intake of either 24 mg (2-mg gum) or 48 mg (4-mg gum). The relative blood levels observed in this study suggest that delivery of nicotine from gum is less than complete.

The first problem is the release of nicotine from the gum. Extraction of nicotine, the difference between the dose and the amount remaining in the gum after chewing for 20 min, was only 53% for the 2-mg gum and 72% for the 4-mg gum. The difference in extraction between dosage strengths may be related to the fact that the 4-mg gum tends to cause more salivation than the 2-mg gum.

Even at this degree of extraction the 4-mg gum should deliver about 34 mg nicotine per day or about the same amount of nicotine as derived from smoking, unless other losses are incurred. The investigators found that in addition to an unextracted residue of about 28% of the dose, another 25% was expectorated, and an additional 25% was swallowed. Nicotine is rapidly absorbed from the gastrointestinal tract but is subject to a large first-pass effect.

Assuming complete absorption (and no first-pass effect) from the oral cavity of extracted nicotine and a 70% first-pass effect for swallowed material, one may calculate that only 1.2 mg of the 4 mg in the gum is available to the systemic circulation. This corresponds to an effective daily dose of only 14-mg nicotine or less than half that derived from smoking cigarettes. These calculations are consistent with the relative blood level data. Despite the relatively poor absorption characteristics of the dosage form, nicotine gum is helpful to people who are trying to stop smoking.[193]

An interesting technique for the administration of a bronchodilator aerosol, fenoterol, in children with asthma, ranging in age from 3 months to 9 years, has been described.[194] Rapid and effective bronchodilation was obtained in most patients simply by directing the jet of the aerosol onto the buccal mucosa. This technique could prove useful in the treatment of young children who cannot use an aerosol dosage form in the recommended manner.

The idea of a buccal spray has been applied to nitroglycerin.[195] An oral nitroglycerin aerosol spray is marketed in the US for prevention and treatment of angina pectoris. The oral spray is available in canisters dispensing 200 metered aerosolized doses of 0.4 mg nitroglycerin. It is sprayed onto or under the tongue. Significant effects on exercise tolerance and heart rate were detected at 2 min after use of the spray.

Some patients may find it easier to use the spray than to open a bottle and remove a small sublingual tablet. Because a dry mouth can delay the dissolution of sublingual nitrate tablets, the aerosol droplets may be better absorbed in some patients. The 3-yr shelf-life of the spray is also an advantage over sublingual tablets, which have a shelf-life of 1 yr under ideal conditions and can lose potency rapidly if they are not kept tightly capped in dark glass containers.

Preliminary findings suggesting that lorazepam is more rapidly absorbed after sublingual administration than after IM injection prompted investigators to compare the efficacy of lorazepam as a preanesthetic agent when given by these two routes.[196] Women admitted for dilatation and curettage participated in the study. Two hr before the procedure each patient received a sublingual tablet and an IM injection, one of which was a placebo.

Irrespective of the route of administration, lorazepam produced significant drowsiness and reduced anxiety within 30 min. Patients in the group receiving active sublingual medication, however, were more drowsy at 60 and 90 min after dosing, as compared with the IM group. Furthermore, lack of recall was significantly greater with sublingual lorazepam than with intramuscular lorazepam. Sublingual lorazepam may be superior to IM lorazepam with the additional advantage of no pain or discomfort on administration.

Alprazolam is widely prescribed as an anxiolytic agent and is under investigation for the treatment of panic disorders. Sublingual administration may be a useful alternative for panic disorder patients who cannot swallow tablets or for those who do not have access to water or some other liquid to facilitate swallowing.

Healthy human subjects received alprazolam on two occasions in random sequence. On one occasion a tablet was swallowed with 100–200 ml water; on the other occasion, the tablet was placed under the tongue and held there for 15 min. The peak plasma concentration of alprazolam after sublingual administration was slightly higher than after oral administration (17 versus 15 ng/ml) and the time to peak was reached earlier after the sublingual dose (1.2 versus 1.7 hr). The mean total area under the plasma concentration curve for sublingual ad-

ministration was about the same as that following oral dosage.

Alprazolam absorption following sublingual administration is at least as rapid as after oral administration on an empty stomach, and completeness of absorption is comparable. The two routes appear to be bioequivalent. Sublingual administration, however, may prove to be preferable to oral administration of alprazolam after a meal, when gastric emptying is prolonged and the rate of absorption is reduced.[197]

Hypertensive emergencies require immediate reduction in blood pressure. Most often they are treated with parenteral drugs such as nitroprusside, diazoxide, or labetalol. Effective drugs that can be self-administered would be advantageous. Oral clonidine and captopril have been found useful in this respect, and both oral and buccal nifedipine have been reported to lower blood pressure within 1 hr in patients with dangerously elevated pressures.

Although buccal nifedipine appears to be useful for reducing elevated blood pressure, doubts have been raised as to whether its effects are the result of buccal absorption or, alternatively, the result of swallowing the material contained in the soft gelatin capsule followed by gastrointestinal absorption. To clarify this question, the sublingual absorption of nifedipine was investigated in healthy human subjects and compared with oral administration.[198]

The subjects bit a capsule containing 10 mg nifedipine in solution and were instructed to keep the capsule in the mouth and to avoid swallowing. After 20 min, the material remaining in the mouth was recovered and the mouth was rinsed thoroughly. On a second occasion, the participants bit another capsule of nifedipine, but this time they swallowed the capsule and its contents with water.

After biting the capsule and not swallowing for 20 min, nearly 90% of the dose was recovered from the mouth. Absorption was slow and led to low plasma levels of nifedipine. Median peak plasma concentration after sublingual administration was 10 ng/ml, reached at 45 min after biting the capsule. After biting and swallowing the capsule, the median peak plasma concentration was 71 ng/ml. The relative bioavailability of nifedipine after sublingual compared with oral administration was only 17%.

The favorable therapeutic results obtained with sublingual administration of nifedipine are probably due to swallowing the drug. If a fast onset of action of nifedipine is desired, the patient should be instructed to bite a capsule and to swallow the contents with water. This will ensure rapid absorption and high levels of the drug.

Relatively few bioavailability studies have been reported for drugs in sublingual dosage forms. The peripheral vasoconstriction effects of ergotamine, 0.25 mg intramuscularly and 2 mg sublingually, and a sublingual placebo were compared by means of plethysmography in normal subjects.[199] There were no significant differences between the ergotamine preparations; both were significantly more active than placebo. Winsor concludes that the two forms at the appropriate doses should be equally effective in the treatment of migraine.

The absorption of methyltestosterone was compared in healthy subjects after administration of 10- and 25-mg tablets and an aqueous solution containing 10 mg of methyltestosterone, all of which were swallowed, as well as after administration of 5 and 10 mg sublingual tablets.[200] The extent of absorption per mg of dose for 25-mg tablets, 10-mg tablets, 10 mg sublingual tablets, and 5 mg sublingual tablets, relative to the oral solution, was 0.90, 0.95, 1.42, and 1.63, respectively. The sublingual tablets produced significantly higher methyltestosterone levels in the serum per mg of dose than did the other dosage forms. These results clearly demonstrate the potential advantage of sublingual administration and the avoidance of presystemic metabolism.

Similar findings have been reported with isosorbide dinitrate.[201] Peak concentrations following 5 mg sublingual or oral doses of the drug were 8.9 and 3.1 mg/ml, respectively (Fig. 6–11).

RECTAL ADMINISTRATION

Certain drugs are given rectally, usually in the form of enemas or suppositories, for local therapy or for systemic effect. The rectal administration of drugs intended for systemic effect is usually limited to those situations in which oral administration is difficult or contraindicated. Suppositories are used more frequently in children than in adults and are a far more important dosage form in Europe than in the United States. Drugs that are administered by this route include aspirin, acetaminophen, indomethacin, theophylline, chlorpromazine, prochlorperazine, cyclizine, promethazine, and certain barbiturates and other anticonvulsive drugs.

Absorption across the rectal mucosa occurs in

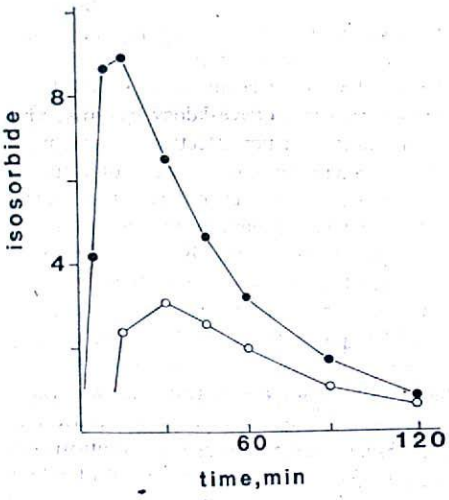

Fig. 6–11. Isosorbide concentrations in plasma following a 5-mg sublingual (●) or oral (○) dose. (Data from Assinder, D.F., Chasseaud, L.F., and Taylor, T.[201])

the same manner as in other parts of the alimentary tract. Although the rectum has a good blood supply, it is devoid of villi and has a relatively small surface area. Hence, drug absorption from the rectum is often slow. Wagner has proposed the following general principles with respect to drug absorption following rectal administration to man:[202] (1) Absorption from the rectum is usually more rapid and more efficient when drugs are given in solution form (microenemas) than in suppository form. (2) Absorption is generally more variable when drugs are administered in solution form rectally than in solution form orally. (3) The presence of fecal matter in the rectum retards absorption. Absorption is more rapid and efficient if a cleansing enema precedes drug administration. (4) Some suppository bases, such as polyethylene glycols (PEG), are irritating to the human rectum and tend to promote defecation and loss of the drug. (5) Bioavailability from suppositories may be poor because the drug is not released or is slowly released.

The pH of a rectal solution may also influence absorption. A dramatic improvement in the rectal absorption of morphine was reported in going from a rectal solution at pH 4.5 to one at pH 7.4.[203] The peak concentration of morphine went from 10 ng/ml to 24 ng/ml and the area under the concentration-time curve increased by about 50%. Side effects, including nausea and sedation, were observed after the more alkaline solution but not after the rectal solution buffered to pH 4.5. These findings are consistent with pH-partition theory.

Rectal administration of theophylline suppositories in the treatment of children with bronchial asthma is questionable. Several studies have concluded that rectal absorption of theophylline from suppositories is slow and erratic.[204,205] Better success has been found with retention enemas of the drug.[206] A clinical study in asthmatic children indicated that adequate serum levels, comparable to those found after a 20-min intravenous infusion of theophylline, can be obtained after a single rectal dose of the drug in aqueous solution.[207] A comparative bioavailability study of oral and rectal solutions of theophylline found that the drug was more rapidly absorbed from oral solutions, as indicated by the peak concentration (7.3 vs 4.9 μg/ml) and the time to peak (1 hr vs 2 hr). On the other hand, the extent of absorption of theophylline after rectal administration was very good, about 90% that found after oral administration. These findings suggest that rectal solutions of theophylline are a reasonable alternative when oral dosing is not possible or desirable.[208]

Attempts to develop rectal dosage forms of tetracycline or penicillin G have been unsuccessful because of the intrinsically poor absorption of these drugs across the rectal mucosa. Studies in healthy subjects indicate that the absorption of tetracycline hydrochloride and sodium penicillin G after rectal administration of aqueous solutions is only about 10% that observed after oral administration of drug solutions to fasting subjects.[209]

The rectal absorption of the antibiotic lincomycin has been studied in children and adults.[210] The extent of absorption of lincomycin in children after rectal administration of an aqueous solution was only 50% that observed after oral administration of a syrup form of the drug and was considerably more variable.

The absorption of lincomycin after rectal administration of an aqueous solution to adults who were given an enema to cleanse the lower colon and rectum the night before was comparable to that observed after oral administration of a capsule of the drug. The bioavailability of lincomycin from the rectal solution in subjects who had not received an enema was only 70% relative to the oral capsule. The absorption of the drug from polyethylene glycol suppositories was poor and erratic. The bioavailability of lincomycin from the suppository was

only about one third that found with the capsule given orally.

The polyethylene glycol suppositories used in these studies were apparently irritating; 4 of 12 subjects had bowel movements within 2 hr after administration. Moreover, a linear correlation was found in 11 of the 12 subjects between the area under the serum concentration-time curve of lincomycin (relative bioavailability) and time from insertion of suppository to first bowel movement (retention time).

Attaining an adequate retention time may be a problem in some patients, regardless of the suppository base. Studies in children with a commercially available cocoa butter suppository containing 5 grains of aspirin produced retention times ranging from 2 to 44 hr.[211] The availability of aspirin in 4 children who retained the suppository for 5 hr or less ranged from 54 to 64% of the dose. More than 80% of the dose of rectal aspirin was absorbed in 4 children who retained the suppository for 10 hr or more. Slow absorption of aspirin from this product was also found in adults. Attempts to improve the absorption of aspirin from rectal suppositories have been frustrated because of the strong association between rapid absorption of aspirin from the rectum and the incidence of local side effects.[212] The investigators concluded that it is difficult to formulate a rectal dosage form of aspirin combining good tolerance with acceptable bioavailability.

There is continued interest in the development of rectal dosage forms of other antipyretic and/or analgesic drugs. Studies in patients with elevated rectal temperature find that rectal acetaminophen suppositories are significantly more effective in reducing fever than placebo, but only 60% as potent as the oral form of the drug.[213] Other studies in febrile children, ranging in age from 3 months to 6 years, indicate that rectal suppositories containing a dose of 15 to 20 mg/kg acetaminophen produce an antipyretic effect almost equal to an oral elixir of the drug and offer an alternative in those children for whom oral administration is not possible.[214]

The absorption of the nonsteroidal anti-inflammatory and analgesic drug naproxen after rectal suppository is almost as rapid and complete as after the commercial oral tablet.[215] The bioavailability of the drug in the suppositories was 95% that of the tablets. When indomethacin is given orally as capsules or rectally as suppositories, 100 mg nightly doses are equally effective in relieving morning symptoms in patients with rheumatoid arthritis.[216] The mean plasma indomethacin concentration was 200 ng/ml during the oral dosing, and 220 ng/ml during the rectal dosing. No differences were seen in side effects or patient preference of the dosage forms.

Rectal suppositories of oxymorphone have been compared with intramuscular injections of the drug in patients with postoperative pain.[217] Rectal administration resulted in lower and delayed peak analgesia and a slightly longer duration of effect than intramuscular administration. When total effect was considered, rectal oxymorphone was found to be one tenth as potent as the intramuscular form.

Allopurinol lowers uric acid levels and is used for the treatment of gout. More recently, allopurinol has also been used prophylactically in patients who are going to receive cytotoxic drugs, to prevent the development of hyperuricemia and consequent uric acid nephropathy. Although allopurinol is usually administered orally, the development of nausea and vomiting among patients undergoing cancer chemotherapy frequently precludes the use of oral tablets. Several cancer centers have used extemporaneously prepared suppositories containing allopurinol to overcome this problem.

Investigators measured allopurinol and oxipurinol, an active metabolite, concentrations in plasma after intravenous, oral, and rectal administration of allopurinol.[218] The rectal dosage form was a suppository prepared by grinding the oral tablets into a fine powder and incorporating the powder into cocoa butter. The bioavailability of the tablet given orally was about 67% but no measurable plasma levels of allopurinol or oxipurinol were found in any subject after rectal administration. The use of rectal suppositories of allopurinol as an adjunct in cancer chemotherapy should be re-examined.

Another example of poor bioavailability after the administration of an extemporaneously prepared suppository has been reported with tamoxifen, a drug used in the management of breast cancer.[219] The mean bioavailability of the suppositories was less than 30% relative to oral tablets of tamoxifen. Whether the findings with allopurinol and tamoxifen reflect poor absorption in the lower bowel or slow release from the formulation is not clear. Under any circumstances, however, extemporaneously prepared suppository formulations must be evaluated with regard to bioavailability before they

are widely used in the institution as an alternate dosage form.

There has been substantial interest in the development of rectal dosage forms of anticonvulsants, particularly diazepam, for children and adults. The bioavailability of diazepam from rectal suppositories is better than from intramuscular injections but not comparable to oral administration.[220,221] On the other hand, diazepam absorption from rectal solutions is far better than from suppositories, and the rate of absorption of the drug from rectal solutions is greater than from oral tablets.[221] Rectal administration of diazepam solution may be a suitable alternative to intravenous injection in young children with convulsive disorders, but additional efficacy studies are required before this approach can be recommended.[222,223] Although high, possibly anticonvulsant, blood levels are achieved after rectal solutions, considerable variability is observed, perhaps related to difficulties in administration.

A more recent report concerned the absorption of single doses of diazepam in adult epileptic subjects following intravenous, oral, and rectal administration.[224] No dosage form produced diazepam concentrations comparable to those found after rapid intravenous injection, concentrations known to be effective in the treatment of status epilepticus. Diazepam oral tablets and rectal solution produced similar peak levels after delays of 15–90 min; the levels were, on average, about half those observed after intravenous administration. Serum diazepam levels above 400 ng/ml, thought to be necessary for a satisfactory anticonvulsant effect, were reached in only a few subjects after rectal administration.

Another study examined the absorption of diazepam after rectal administration in children with epilepsy.[225] When given as a rectal solution, diazepam was rapidly absorbed, resulting in serum concentrations above 200 ng/ml within 10 min in most children. The investigators suggest that this route of administration and dosage form may be an effective alternative to intravenous administration. A commercial suppository formulation of diazepam, on the other hand, was absorbed slowly and not recommended for urgent treatment of seizures.

The results of a clinical trial of single dose rectal and oral administration of diazepam 20 mg for the prevention of serial seizures in adult epileptic patients has also been reported.[226] Diazepam was given rectally as a new suppository formulation with rapid release characteristics immediately after a seizure and was effective in preventing recurrent seizures within a 24-hour observation period. The suppository produced a wide range of diazepam levels in serum; the mean serum concentration at 60 min was 190 μg/ml. In a similar study, oral administration of diazepam also reduced the incidence of serial seizures compared with a placebo. The mean 60 min serum diazepam level was 273 ng/ml.

Intravenous secobarbital has been used in the emergency treatment of acute convulsive conditions. Some epilepsy centers have explored the use of rectal secobarbital as adjunct therapy in poorly controlled epileptic children. Sodium secobarbital suppositories were prescribed for home use in children who frequently had prolonged seizures. Parents were instructed to administer the suppository when their child had a seizure that lasted more than 15 min. The availability of this dosage form offered the possibility of aborting seizures and obviating the need to bring the child to the hospital emergency room.

The absorption of rectal secobarbital was studied in epileptic children.[227] Some subjects received a rectal solution of secobarbital and the others were given secobarbital suppositories. The peak serum concentration of secobarbital was consistently higher and occurred earlier in children given the solution rather than the suppository. The extent of absorption, however, was about the same for both dosage forms. If rectal secobarbital is considered for treatment of prolonged seizures, a rectal solution may offer a more rapid and consistent onset of effect than a suppository.

Clinical studies suggest that rectal valproate may also be useful in the treatment of epilepsy. The bioavailability of sodium valproate after repeated administrations of rectal suppositories was studied in epileptic children and adolescents on chronic valproic acid therapy.[228] Some patients were treated with repeated doses of an oral solution and others with an enteric coated tablet of valproate. Serum levels of valproic acid were determined at steady state. Thereafter, suppositories were given regularly instead of the oral dosage forms; serum levels were again measured after several days of dosing.

Average steady-state concentrations of valproic acid were about the same for all three dosage forms, suggesting bioequivalence with respect to extent of absorption. Serum level-time profiles were nearly

identical for the oral and rectal solutions. Steady-state serum levels during oral administration of enteric-coated tablets showed less fluctuation than those measured after the oral or rectal solution, suggesting slower absorption.

Intravenous metronidazole is widely used for prophylaxis and therapy of anaerobic infections in abdominal and gynecologic surgery, but the cost of this therapy is high; equally effective but less expensive alternative dosage forms are sought. Clinical investigators in Australia have reported that rectal administration of metronidazole suppositories provides adequate therapeutic plasma levels of the drug after surgery; they suggest that use of suppositories could result in a significant decrease in drug costs.[229] An earlier study indicated that the bioavailability of metronidazole from a rectal suppository was about 90% relative to an oral tablet of the drug.[230]

Rectal solutions of corticosteroids are used in the treatment of inflammatory bowel disease, but there is controversy as to whether their effect is local or systemic. The idea of a local effect has gained favor because early studies claimed poor absorption of corticosteroids after rectal instillation. More recent investigations challenge this idea. Prednisolone appears in the plasma of patients with ulcerative colitis after administration of prednisolone-21-phosphate retention enemas.[231] Blood levels of prednisolone are similar after oral or rectal administration of the drug. These findings suggest that 20 mg prednisolone given by retention enema may exert systemic effects. About 50 to 90% of a dose of hydrocortisone is absorbed from a rectal solution of the drug, if the retention time exceeds 8 hr.[232] On the other hand, the relative bioavailability of methylprednisolone is only 14% after a rectal solution of methylprednisolone acetate, suggesting that the drug may act locally rather than systemically (Fig. 6–12).[233]

An enema containing mesalamine (5-aminosalicylic acid) is available for treatment of mild to moderate distal ulcerative colitis.[234] Severe ulcerative colitis is treated with systemic corticosteroids and less severe disease is usually treated with oral sulfasalazine and/or corticosteroid enemas. Sulfasalazine, a prodrug hydrolyzed to sulfapyridine and mesalamine in the lower bowel, is effective but many patients must discontinue the drug because of adverse effects.

Most authorities believe that the active component of sulfasalazine is mesalamine and that most

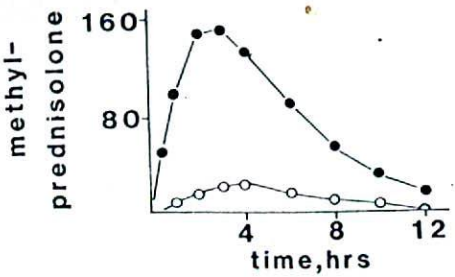

Fig. 6–12. Methylprednisolone concentrations in plasma (ng/ml) following single oral (●) or rectal (○) dose of methylprednisolone acetate. (Data from Gary, D.C., et al.[233])

or all of its toxicity is due to sulfapyridine. Oral mesalamine, however, is rapidly absorbed in the small intestine and little if any of the dose reaches the colon. Accordingly, dosage forms designed to deliver mesalamine to the lower bowel are under investigation. Mesalamine enema is the first of these products to be approved in the US.

It is generally appreciated that the formulation can markedly affect the absorption of drugs from rectal suppositories. Accordingly, there is a potential for clinically important differences in bioavailability among commercially available products. Unfortunately, few clinical studies on this question have been reported. The bioavailability of salicylate from 5 brands of aspirin rectal suppositories was compared to oral administration of the drug in a tablet.[235] When the products were retained for longer than 10 hr, absorption was essentially complete; however, when retention was limited to 2 hr, the absorption of aspirin from one product was 40% of the dose whereas only 20% of the dose was absorbed from the others. Thus, substantial differences in the rate of aspirin absorption exist among marketed rectal suppositories.

The bioavailability of acetaminophen after rectal administration of three acetaminophen suppository formulations obtained from hospital and commercial sources was compared to that after oral administration of a tablet dosage form.[236] The absorption of acetaminophen from the three rectal products ranged from 68 to 88% relative to the tablet. As shown in Figure 6–13, the absorption rate varied markedly among products. The acetaminophen in one formulation was so slowly absorbed that the clinical value of the product is questionable.

There has been renewed interest in the rectal

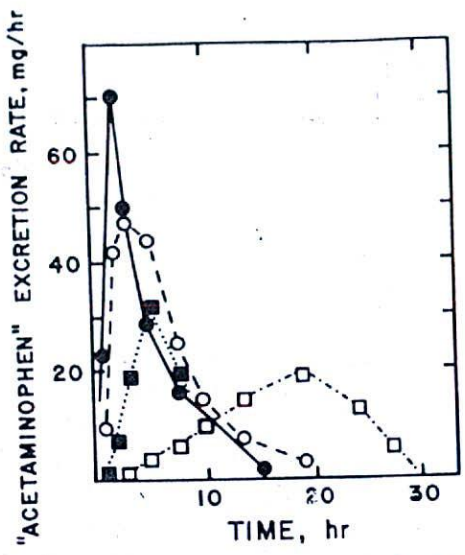

Fig. 6–13. Urinary excretion of unchanged and metabolized acetaminophen ("acetaminophen") after oral administration of a tablet (●) or after rectal administration of different suppositories (○,■,□). (Data from Feldman, S.[236])

administration of drugs with the realization that it may result in improved bioavailability by avoiding first-pass hepatic metabolism. Parts of the rectum are perfused by the inferior and middle hemorrhoidal veins, which do not drain into the portal system. On the other hand, the superior hemorrhoidal vein enters the hepatic portal circulation by way of the inferior mesenteric vein.

Rectal administration of the investigational analgesic meptazinol in healthy subjects resulted in more rapid and complete absorption than after oral administration.[237] The more rapid absorption may be the result of avoiding the delayed gastric emptying seen after oral administration of the drug. The more complete absorption suggests that at least part of the rectal dose was absorbed directly into the systemic circulation and not subject to presystemic hepatic metabolism.

Blood levels of lidocaine were determined in healthy subjects following 200 mg intravenous, 300 mg oral, and 300 mg rectal doses of the drug. The mean bioavailability of lidocaine was considerably higher after rectal than after oral administration (63% vs 31%). Analysis of the data suggests that about half of the rectal dose bypasses the liver during absorption.[238] These findings suggest that, in principle, it is possible to partially avoid first-pass hepatic metabolism by giving a drug rectally.

In another study, investigators found that rectal propranolol resulted in a different metabolite pattern than that observed after oral or intravenous administration of the drug.[239] The ratio of metabolite to parent drug in plasma after rectal propranolol was always larger than after intravenous administration but smaller than after oral dosing. This suggests partial avoidance of first-pass metabolism by the rectal route, consistent with earlier results.

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