Biopharmaceutics and Clinical Pharmacokinetics

MILO GIBALDI, PH.D.

Dean, School of Pharmacy
Associate Vice President,
Health Sciences
University of Washington
Seattle, Washington

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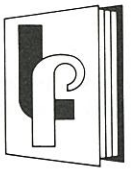

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Prolonged-Release Medication

PHARMACOKINETIC THEORY

The duration of drug effect is a function of the pharmacokinetics of the drug molecule in an individual patient. The clearance and apparent volume of distribution of a drug determine the degree of persistence of the molecule in the body. This persistence is characterized in terms of half-life or mean residence time (MRT). Because the duration of drug action is related to the distribution and elimination kinetics of a drug, the frequency of dosing must also bear some relationship to the drug's half-life or MRT.

We often find that the frequency of dosing needed to maximize the benefit-to-risk ratio of a drug is unreasonable. For example, in most patients, procainamide must be given every 3 to 4 hr around the clock to assure continuous suppression of irregular cardiac rhythms. The same dosing requirements apply to the use of the bronchodilator theophylline in children. The optimum use of idoxuridine eye drops for herpetic keratitis calls for hourly administration.

A particularly conscientious patient may be able to comply with these requirements during the waking hours, but even he is confounded during the sleep period. Excessively frequent dosing requirements do not encourage compliance to the prescribed drug regimen, particularly when the drug is used prophylactically or to treat a silent disease such as hypertension.

The alternative solutions to this important therapeutic problem include giving the drug less frequently and accepting a less favorable therapeutic outcome, seeking new drugs with similar pharmacologic effects but more favorable pharmacokinetic characteristics, or developing a prolonged-release dosage form. In most cases, experience dictates that the pharmaceutical solution be examined first.

Drug Absorption and Duration of Effect

Prolonged-release medication is a dosage form containing more drug than a conventional dosage form but releasing the drug far more slowly, over a period of hours or even days rather than seconds or minutes. In essence, we seek a situation where the duration of drug action is substantially determined by the duration of drug release from the dosage form rather than the drug molecule's pharmacokinetic properties.

This idea can be expressed mathematically by considering the intravenous and oral administration of a drug that distributes rapidly from the bloodstream. After intravenous bolus administration, drug concentration in the blood is given by:

$$C = C_o \exp(-kt) \qquad (7\text{–}1)$$

where C_o is the initial drug concentration and k is the first-order elimination rate constant. Under these conditions, MRT is given by:

$$MRT_{iv} = 1/k \qquad (7\text{–}2)$$

The persistence of drug in the body and the duration of drug effect is a function of drug elimination kinetics.

Following oral administration of the drug, assuming first-order absorption, concentration in the blood is given by:

$$C = C^*F[\exp(-kt) - \exp(-k_a t)] \qquad (7\text{–}3)$$

where C* is a complex constant, F is the fraction of the oral dose reaching the systemic circulation, and k_a is the first-order absorption rate constant. The MRT is given by the following equation:

$$MRT_{oral} = MRT_{iv} + 1/k_a \qquad (7\text{–}4)$$

The time course of drug concentration in the blood is affected by the absorption process, i.e., $MRT_{oral} > MRT_{iv}$. But, for most drugs, absorption from conventional dosage forms is so rapid that MRT_{oral} is not substantially greater than MRT_{iv}. Accordingly, even after oral administration the duration of effect is largely a function of the elimination kinetics of the drug.

However, if the release rate of drug from the dosage form is decreased (i.e., decrease k_a), we simultaneously increase MRT_{oral}. The MRT becomes more dependent on the release rate and less dependent on the drug molecule's kinetics. Using this approach, a situation is reached where the MRT and the duration of effect are largely controlled by the release rate of drug from the dosage form.

Frequency of Dosing and Therapeutic Index

The *therapeutic index* of a drug is most usefully defined in man as the ratio of the maximum drug concentration in blood that can be tolerated to the minimum drug concentration needed to produce a satisfactory clinical response. Therapeutic concentration ranges for certain drugs in man have been identified. In some cases, these ranges are narrow, resulting in small therapeutic indices.

The average therapeutic range of theophylline concentration in blood is about 8 to 20 μg/ml; the therapeutic index of theophylline is 2.5. Estimates of therapeutic index for other drugs are 2.0 for digoxin and valproic acid, 2.7 for procainamide, and 4.0 for lidocaine. We seek to maintain drug concentrations in blood well within the therapeutic range during drug therapy. This requires not only the selection of an appropriate daily dose; the drug must also be given with sufficient frequency so as to minimize the range of blood concentrations that are produced. The ratio of maximum to minimum drug concentrations at steady state should not exceed the therapeutic index of the drug. This concentration ratio is a function of the half-life of a drug and the frequency of dosing.

For drugs that are both absorbed and distributed rapidly, Theeuwes and Bayne[1] have demonstrated the following relationship:

$$\tau < t_{1/2} (\ln TI)/(\ln 2) \qquad (7\text{–}5)$$

where τ is the dosing interval, $t_{1/2}$ is the half-life, and TI is the therapeutic index. A drug with a therapeutic index of 2 and a half-life of 3 hr must be given no less frequently than every 3 hr to avoid excessive or subtherapeutic concentrations. A drug with a similar half-life but a therapeutic index of 4 may be given every 6 hr.

When drug effects are directly related to concentration in blood but distribution is slow, the drug must be given even more frequently than suggested by Equation 7–5. In such cases, a better estimate of dosing interval may be obtained by replacing $t_{1/2}$ with 0.693(MRT) where MRT is the mean residence time.

Steady-State Concentrations and Release Rate

Dosing regimens for rapidly absorbed drugs are a function of the pharmacodynamic and pharmacokinetic characteristics of the drug molecule; they must be based on the therapeutic index and half-life or MRT of the drug itself. Reducing the absorption rate of a drug by controlling its release rate from the dosage form, however, can dramatically affect drug concentrations at steady state. For a given dosage regimen, the slower the release rate of drug, the smaller is the ratio of maximum to minimum drug concentrations at steady state. Under these conditions, we can give larger doses at less frequent intervals and still stay within the therapeutic concentration range of the drug; this is the rationale for prolonged-release medication.

Prolonged-release medication offers obvious advantages for drugs with short half-lives and small therapeutic indices. These specialized dosage forms permit such drugs to be given at more reasonable intervals throughout the day; implications include more optimal therapy, patient convenience, and improved patient compliance with the prescribed regimen. The application of prolonged-release medication, however, is not limited to such drugs. Since these dosage forms offer the potential of reducing the peak-to-trough drug concentration ratio, they may be useful for many more drugs.[2]

Reducing the peak-to-trough concentration ratio has been found to improve the benefit-to-risk ratio of some drugs. The potassium-depleting effect of hydrochlorothiazide disappears, while its diuretic effect is slightly enhanced, when the drug is given every 3 hr rather than once a day.[3] The nephrotoxicity of gentamicin is substantially reduced when steady-state concentrations are maintained in a narrow range of about 1 to 4 μg/ml.[4] The safety of certain anticancer drugs, including bleomycin[5] and methotrexate,[6] is increased when given continuously by infusion rather than intermittently.

By minimizing fluctuations in blood levels we may be able to reduce the dosage required, improve the effectiveness, and decrease the adverse effects of a drug. For instance, pilocarpine administered continuously by an ocular insert reduces elevated intraocular pressure in patients with glaucoma without the marked myopia commonly seen in patients using pilocarpine eyedrops every six hours.

White[7] compared intraoperative and postoperative effects of fentanyl and ketamine administered by continuous intravenous infusion with those produced by intermittent iv bolus doses. Continuous infusion minimized the peaks and valleys of drug concentration in blood and, presumably, brain that ordinarily result from intermittent dosage.

Women scheduled for elective outpatient gynecologic surgery received either fentanyl or ketamine as an intravenous adjunct to nitrous oxide for maintenance of general anesthesia after induction with thiopental. The drugs were given either by continuous iv infusion or intermittent iv bolus. The method of drug administration resulted in important differences.

Only about one-half the dosage of fentanyl or ketamine was needed to maintain anesthesia when the drugs were given by continuous infusion rather than by intermittent bolus. The use of less drug resulted in more rapid recovery from anesthesia and in substantially less postoperative sedation, and minimized postoperative psychomotor dysfunction. Excessive sedation was noted in about 50% of the patients in the bolus groups but in less than 10% of the patients in the infusion groups.

Continuous infusion also improved intraoperative conditions. Respiratory depression and muscular rigidity occurred less frequently with continuous rather than intermittent administration of fentanyl. Hypertension and tachycardia occurred less frequently with continuous rather than intermittent ketamine.

Zero-Order Release

Continuous, constant-rate intravenous infusion leads to constant blood levels. Under these conditions, blood levels are invariant with time; there are no peaks or troughs. Provided that the constant drug concentration is within the therapeutic range, this is an ideal situation for many drugs. The only way to achieve constant blood levels is to administer the drug at a constant (zero-order) rate over the entire dosing interval. The concentration of drug at steady state is given by the following equation:

$$C_{ss} = k_o/Cl \qquad (7\text{–}6)$$

where k_o is the zero-order delivery or release rate of drug, and Cl is the clearance of the drug. Fluctuations in blood levels do occur under these conditions, because of temporal variations in clearance or in the delivery rate, but they are usually small.

Until recently, constant rate intravenous infusion, by means of a carefully controlled drip or mechanical pump, was the only way to attain constant blood or tissue levels of drug. Today, there are dosage forms intended for oral, ocular, intravaginal, or intramuscular administration that release drug in a zero-order or near zero-order fashion. These dosage forms are discussed in other sections of this chapter.

ORAL MEDICATION

Most prolonged-release dosage forms are intended for oral administration. A prolonged-release dosage unit contains more drug than a conventional dosage unit but is intended to be given less frequently. A drug that is ordinarily given at a dose of 250 mg 4 times a day in a conventional tablet or capsule may be given at a dose of 500 mg twice a day, or 1 g once a day, in a prolonged-release dosage form. The ultimate criteria for evaluating such dosage forms are: (1) the amount of drug intended to be absorbed is indeed absorbed in a predictable and consistent manner; and (2) the steady-state ratio of maximum to minimum drug concentrations is no greater than or, optimally, less than that produced by the more frequently administered conventional dosage form.

The early history of the prolonged-release oral dosage form is probably best forgotten. Products were developed empirically, often with little rationale, and bioavailability problems were common. Many people viewed these dosage forms as little more than marketing inducements. Today, the situation has improved; many of the available products are well designed drug delivery systems and have a defined therapeutic goal. In some cases, the prolonged-release dosage form is the most important and most frequently used form of the drug.

A wide variety of techniques have been used to develop prolonged-release oral dosage forms. These techniques include the use of drug substances of decreased solubility or dissolution rate, accomplished by increasing particle size or substi-

tuting less soluble salts or complexes, ion exchange resins to bind the drug substance, porous, nondisintegrating, inert carriers as matrices for the drug, slowly eroding coatings or matrices, and coatings that serve as membranes for drug diffusion.

Most oral prolonged-release dosage forms can be characterized as either subdivided or single units. Subdivided prolonged-release dosage forms, exemplified by the hard gelatin capsule containing numerous drug-impregnated beads, present the drug to the gastrointestinal tract in the form of many slowly-dissolving particles or granules. Often, several kinds of beads are found in the capsule, some releasing the drug rapidly, others releasing the drug over a period of several hours, still others releasing the drug at intermediate rates. Spansule is a trade name historically associated with this dosage form. More details of these and other formulations can be found in a recent review by Longer and Robinson.[8] Phenothiazines, antihistamines, iron, and many other drugs are available in this kind of dosage form. In general, the release and absorption of drugs from slow-release beads can be described by first-order kinetics.

The single-unit prolonged-release dosage form remains more or less intact throughout the gastrointestinal tract, releasing the drug continuously during its passage down the tract. An example of this dosage form is the inert plastic matrix, a dosage form that has been used widely in Europe. The drug is mixed with inert, insoluble, powdered matrix material consisting of plastic resins and other ingredients and compressed. In the gastrointestinal tract, drug particles from the surface of the matrix system dissolve and leave pores through which drug from within the tablet leaches out. The matrix retains its shape during the leaching process and is eliminated in the feces. The release rate of drug decreases with time and, in this sense, resembles a first-order process.[9]

The steady-state plasma levels and pharmacologic effects of a daily dose of 0.2-g metoprolol, a cardioselective β-blocker, in a prolonged-release matrix tablet and in regular 0.1-g tablets were studied in healthy subjects. The following dosing regimens were used: (1) one prolonged-release tablet once a day; (2) two 0.1-g regular tablets once a day; and (3) one 0.1-g regular tablet every 12 hr. The peak-to-trough concentration ratio of metoprolol was, on the average, about 10 for the matrix tablet and the twice-a-day regimen and about 40 for the once-a-day administration of the regular tablets (Fig. 7–1). Metoprolol in the matrix tablet produced a more uniform effect on heart rate and systolic blood pressure during exercise than the corresponding daily dose of metoprolol given as two 0.1-g tablets once daily or as one 0.1-g tablet twice a day.[10] Although metoprolol has a relatively short half-life, about 3 hr, a once-a-day regimen can be developed with a prolonged-release dosage form. The same is true for propranolol.[11]

Some pharmaceutical scientists judge subdivided prolonged-release dosage forms to be potentially safer than intact or single-unit dosage forms because a mechanical failure of the coating or matrix would result in the immediate release of only a small fraction of the entire dose. Mechanical failure is unlikely to occur with the matrix tablet, but it may occur in those single-unit dosage forms that rely on a continuous membrane to control release. A failure in this case may result in the immediate dumping of the entire dose, a quantity of drug that is 2 or 3 times the amount given as a single dose in a conventional dosage form.

Because prolonged-release products are complex dosage forms, substantial differences in performance among different products of the same drug may occur. Although the prolonged-release matrix tablet of metoprolol, previously described, has a longer duration of effect than the same dose of the drug given as regular tablets,[12] this is not true for a different prolonged-release product of metoprolol.[13,14] One product shows a significant improvement over conventional metoprolol whereas the other does not.

Considerable differences among prolonged-release products of theophylline have also been reported. Studies in adult subjects indicate that theophylline is slowly but completely and consistently absorbed from three of six prolonged-release formulations. Theophylline absorption from the other three products is more erratic and less complete.[15] In another study, theophylline absorption from three commercial products labeled as prolonged-release was compared to the absorption from a standard uncoated tablet. Two of the prolonged-release products showed considerably slower absorption of theophylline than did the regular tablet, but the third product did not.[16]

To determine whether clinically important changes in serum theophylline concentrations occur when patients switch their brand of prolonged-release theophylline, 10 subjects with asthma were given the same dose of four different

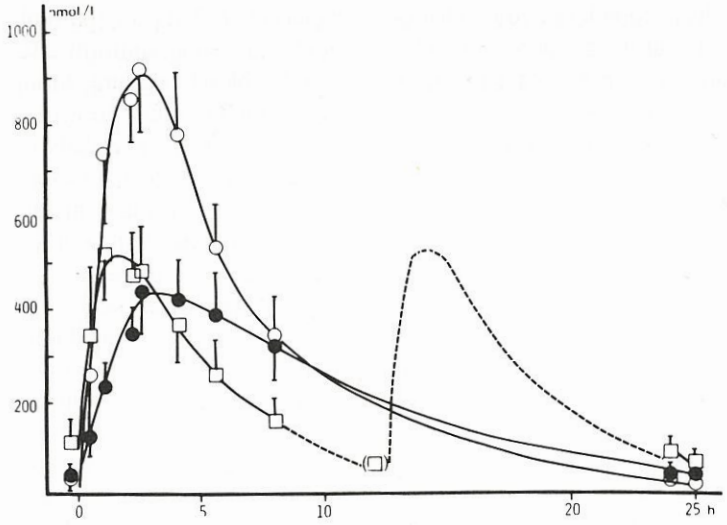

Fig. 7–1. Mean steady-state plasma concentrations of metoprolol after repetitive dosing of a prolonged-release tablet (0.2 g) once a day (●), two 0.1 g regular tablets once a day (○), and one 0.1 g regular tablet every 12 hr (□). (From Johnsson, G., et al.[10])

commercially available products for 2-week periods in a random, double-blinded, crossover fashion.[17]

On at least one occasion in every subject, switching between brands of theophylline resulted in serum theophylline levels outside the accepted therapeutic range, and this was associated with toxic symptoms in 5 of the subjects. Worsening pulmonary function was observed in two subjects when switching resulted in lowered theophylline levels. Many of the changes in theophylline concentrations on switching from one brand to another could not be predicted by the bioavailability differences between the products. The investigators concluded that "these results argue against the open substitution of these formulations and suggest that if patients are switched between different brands of SR theophylline, their serum theophylline concentration needs to be closely monitored."

Much has been published concerning prolonged-release theophylline during the past 10 years. The drug has a relatively short half-life, particularly in children, and a small therapeutic index. Clinical studies suggest that 40% of all children receiving conventional products of theophylline in the usual every 6-hr manner will have excessive or subtherapeutic blood levels of the drug.[18]

Although no well-controlled clinical trials have been published showing that prolonged-release theophylline preparations are more effective than plain theophylline tablets or solutions, many clinicians report that the long-acting formulations are more effective in controlling symptoms, especially during the night. Furthermore, compliance is likely to improve when patients take medication only twice a day, rather than 3 or 4 times a day. On the other hand, some clinicians have found that when adverse effects occur with prolonged-release theophylline, they persist longer. Some patients taking the long-acting preparations complain of insomnia, a known adverse effect of theophylline.

Adult smokers and children, who metabolize theophylline rapidly, may benefit most from treatment with prolonged-release preparations. In many patients, it may be necessary to individualize the daily dose and, in some patients, it may be necessary to give the product more frequently than twice a day.

Individual variability in dosing requirements is clearly seen in the results of a study evaluating one of the more commonly prescribed prolonged-release theophylline preparations, Theodur.[19] In a panel of 20 asthmatic patients, 6 to 18 years of age, receiving the long-acting theophylline product twice a day, the daily doses needed to produce an average blood level of about 15 μg/ml ranged from 6.1 to 16.3 mg/kg. The blood levels resulting from these individualized regimens, as estimated from 4 to 5 blood samples taken over the course of each of 2 consecutive steady-state dosing intervals, showed surprisingly little fluctuation. Peak and trough values and peak-to-trough ratios for the 20

Table 7–1. Peak and Trough Serum Concentrations of Theophylline During 24 hr at Steady State in Children Receiving, on the Average, 10 mg/kg Twice a Day in a Prolonged-Release Product.*

Patient	Peak concn. (μg/ml)	Trough concn. (μg/ml)	Peak-to-trough ratio
1	17.6	10.3	1.7
2	22.7	12.7	1.8
3	17.0	12.0	1.4
4	22.9	14.8	1.5
5	16.4	11.2	1.5
6	18.9	12.4	1.5
7	17.2	7.0	2.5
8	21.8	16.3	1.3
9	13.7	8.7	1.6
10	15.5	12.6	1.2
11	20.3	16.6	1.2
12	18.5	9.0	2.1
13	18.4	10.6	1.7
14	19.7	12.1	1.6
15	17.6	10.5	1.7
16	20.3	15.4	1.3
17	17.5	11.8	1.5
18	23.5	16.7	1.4
19	14.5	7.6	1.9
20	16.8	10.4	1.6

*Data from Kelly, H.W., and Murphy, S.[19]

patients are shown in Table 7–1. Average blood levels are shown in Figure 7–2. If twice-a-day doses of regular theophylline, sufficient to produce average levels of about 15 μg/ml, were given to these patients we would expect to find peak-to-trough concentration ratios of about 10.

A circadian variation in theophylline levels in serum is quite evident during treatment with certain twice-a-day slow-release theophylline products. Steady-state theophylline concentrations for the 12-hr period following the morning dose are different from those following the evening or night dose. In one study, peak concentration at steady state after an 11 AM dose occurred at about 3 hr after dosing, whereas peak level was observed at about 9 hr following the 11 PM dose, which was taken immediately before retiring.[20] The area under the concentration-time curve during a dosing interval at steady state was also smaller after the night dose than following the morning dose. These differences reflect a circadian variation in theophylline absorption rather than in theophylline metabolism.

A change in posture could be a simple explanation of the circadian variation in theophylline pharmacokinetics.[21] This was examined in healthy human subjects who took 450 mg slow-release aminophylline orally at the same time of day on two separate occasions. On one day the subjects remained standing and on the other, they lay supine throughout the study. Theophylline levels in plasma were measured hourly for 6 hr after the dose.

At each sampling time, theophylline levels were higher during the standing experiment than during the supine study. Peak concentration of theophylline with the subjects standing occurred at 5 hr and was 6.4 mg/L. Theophylline levels were ascending for the entire 6-hr study period in the supine group;

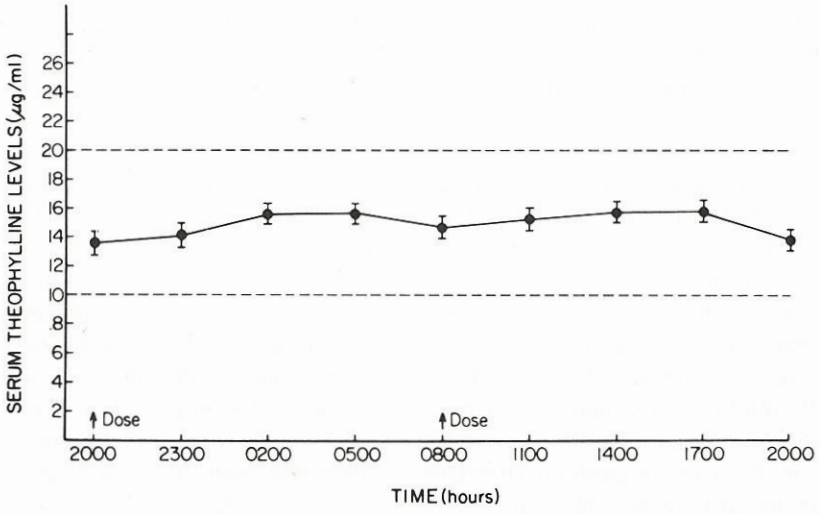

Fig. 7–2. Mean steady-state serum concentrations of theophylline in children receiving an average dosage of 10 mg/kg in a prolonged-release product every 12 hr. (From Kelly, H.W., and Murphy, S.: Efficacy of a 12-hour sustained-release preparation in maintaining therapeutic serum theophylline levels in asthmatic children. Pediatrics, 66:100, 1980. Copyright American Academy of Pediatrics 1980.)

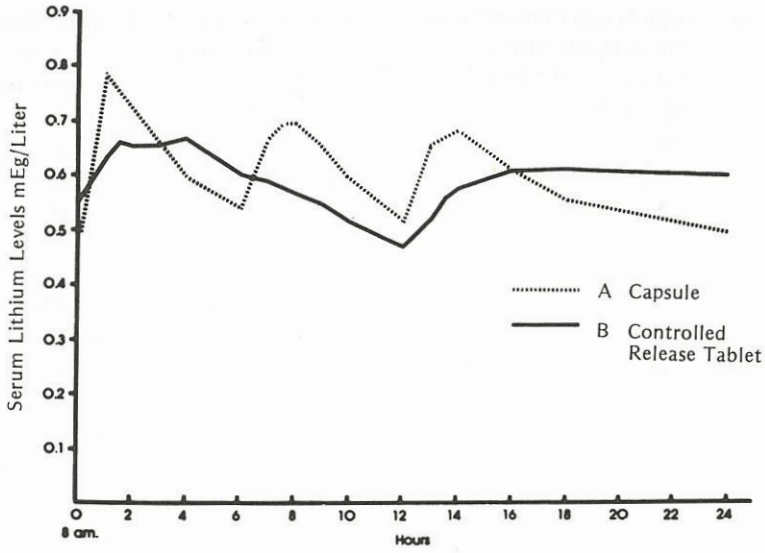

Fig. 7–3. Mean steady-state serum levels of lithium in healthy subjects who received a 300-mg capsule 3 times a day or a 450-mg prolonged-release tablet twice a day. (From Caldwell, H.C., et al.[24])

mean concentration at 6 hr was 5.4 mg/L. The investigators concluded that the supine position assumed at bedtime may be an adequate explanation for the diurnal variation seen with twice-a-day prolonged-release theophylline products.

Theophylline is widely used in children, so it is not surprising that slow-release tablets are sometimes chewed or crushed to facilitate swallowing. This practice may result in a loss of the prolonged-release characteristic of the product. To examine this question, Theo-Dur, a widely used formulation, was given to healthy adult subjects on three occasions, at least 1 week apart.[22] On the first day, subjects were randomly allocated to either swallow intact or chew, and then swallow, a 300 mg tablet. Subjects were then crossed over for the second dose. The effects of crushing the tablet prior to ingestion were studied at the third dose. Swallowing the tablets intact resulted in a significantly longer time to peak concentration compared with chewing or crushing (i.e., 6 hr *vs* about 3 hr) and the peak concentration was somewhat lower, 35.6 μmol/L, compared with chewing (43.1 μmol/L) or crushing (41.9 μmol/L). Area under the curve, however, was about the same for all three modes of administration. Chewing or crushing Theo-Dur tablets does not appear to have a substantial effect on the bioavailability characteristics of the product, suggesting that it may be a suitable preparation for use in young children.

A prolonged-release liquid theophylline preparation, aimed at the pediatric population and designed for twice-daily administration, is under investigation.[23] The suspension was compared with aminophylline solution (administered every 8 hr) in 27 asthmatic children less than 12 years of age. Average steady-state levels of theophylline were about 10% lower during treatment with the suspension than with the solution. Peak levels were also lower (11.2 vs 14.2 μg/ml) and the difference between C_{max} and C_{min} was smaller (6.9 vs 10.0 μg/ml) with the suspension. The investigators concluded that the slow-release suspension should prove to be useful in patients who require maintenance theophylline therapy, but who cannot take solid oral dosage forms.

Lithium carbonate is the drug of choice in treating certain phases of manic depression. Although the drug has a long half-life, about 24 hr, it also has a narrow therapeutic index and must be given 3 or 4 times a day. Steady-state serum level fluctuations of lithium were compared following regular capsules (300 mg 3 times a day) or prolonged-release tablets (450 mg every 12 hr) of lithium carbonate.[24] Average blood levels are shown in Figure 7–3. The degree of fluctuation (Fl) of serum levels was assessed by the following equation:

$$Fl = (C_{max} - C_{min})/\overline{C} \qquad (7\text{–}7)$$

where C_{max} and C_{min} are the maximum and minimum drug concentrations over the 24-hr steady-state dosing cycle, and $\overline{C}$ is the mean concentration

over the cycle. $\overline{C}$ is estimated from the ratio of area under the curve to dosing interval. This fluctuation index is analogous to the coefficient of variation; small values are desired for the prolonged-release preparation. This index may be more stable than the peak-to-trough concentration ratio, which could be highly unstable in the presence of error for small values of C_{min}. In this study, the index was 0.46 for the prolonged-release tablet regimen and 0.66 for the regular capsule regimen, suggesting that the regular product produces about 40% more fluctuation in serum lithium levels than the slow-release formulation.

Fluctuations in serum levels are related not only to the release rate of drug from the dosage form and the frequency of administration (dosage interval), but also vary with drug elimination rate. Steady-state studies with a prolonged-release theophylline product found a linear relationship between percent fluctuation and theophylline clearance in individual subjects.[25]

Weinberger and Hendeles[26] also calculated the percent fluctuation in steady-state serum levels of theophylline for different products. With one prolonged-release product, percent fluctuation was 57% in slow metabolizers of theophylline (half-life = 7.7 hr) but increased to 154% in rapid metabolizers (half-life = 3.7 hr).

Several antiarrhythmic drugs are plagued with the undesirable characteristics of short half-life and narrow therapeutic index. Procainamide is an example; its half-life is about 3 hr. Therapeutic and toxic effects have been related to drug concentrations in plasma. The therapeutic range is 4 to 8 μg/ml but can often extend to 10 μg/ml without toxicity. To maintain safe, adequate blood levels, the regular tablet form of the drug must be given every 3 to 4 hr.

Steady-state levels of procainamide were determined in patients receiving about 20 mg/kg per day in the form of prolonged-release matrix tablets of the drug every 8 hr.[27] Mean procainamide blood levels are plotted in Figure 7–4. In 17 of the 26 patients, blood levels were maintained above a level of 4 μg/ml for at least 75% of the time. Of the 9 patients showing blood levels below the minimum level for more than 25% of the time, 8 would have benefited from an increased daily dose or improved compliance with the regimen. In 4 of the 26 patients, blood levels were above 10 μg/ml for more than 10% of the time. All 4 patients required a lower daily dose and, possibly, more frequent administration. The results suggest that this prolonged-release form of procainamide, given every 8 hr, would benefit most patients if the daily dose were individualized.

Disopyramide is another orally effective antiarrhythmic; its electrophysiologic properties are similar to those of quinidine and procainamide. A therapeutic range of 2 to 4 μg/ml has been suggested for the drug. Because of its short half-life, disopyramide must be given 4 times a day to maintain safe and effective concentrations in plasma. Disopyramide concentrations were determined in plasma following repeated doses of regular capsules (150 mg every 6 hr) or prolonged-release matrix tablets (300 mg every 12 hr) to patients with various kinds of arrhythmia.[28] A level of 4 μg/ml with regular capsules was exceeded by 2 patients, and 1 patient exceeded this level with the matrix tablet. None of the patients had a level below 2 μg/ml. The average steady-state peak-to-trough concentration ratio was 1.4 for the capsules and 1.6 for the prolonged-release tablets. The average fluctuation index was 0.36 for the regular product and 0.43 for the prolonged-release preparation. Although the matrix tablet was given only half as frequently as the regular capsules, little difference in blood levels of disopyramide was noted between products. The matrix tablet of disopyramide appears to be a useful prolonged-release form of the drug.

Drugs absorbed by specialized, capacity-limited transport processes are ordinarily not good candidates for prolonged-release dosage forms. Facilitated absorption is often site-specific and drug released beyond this site in the intestine is usually poorly absorbed. Iron may be an exception. A prolonged-release preparation containing 100 mg of ferrous iron, given twice daily, was compared to a conventional tablet containing 50 mg of ferrous sulfate, given 4 times daily. In patients with iron deficiency anemia, more iron was absorbed from the slow-release preparation.[29]

Prolonged-release forms of drugs such as nitrofurantoin[30] or lithium[31] have been investigated for reducing the incidence of nausea and vomiting resulting from gastrointestinal irritation or high blood concentration peaks. Studies with lithium in human subjects show that rapidly disintegrating tablets generally produce more nausea than do prolonged-release tablets. The incidence of this side effect appears to correlate with high concentrations of lithium in the stomach and proximal intestine.

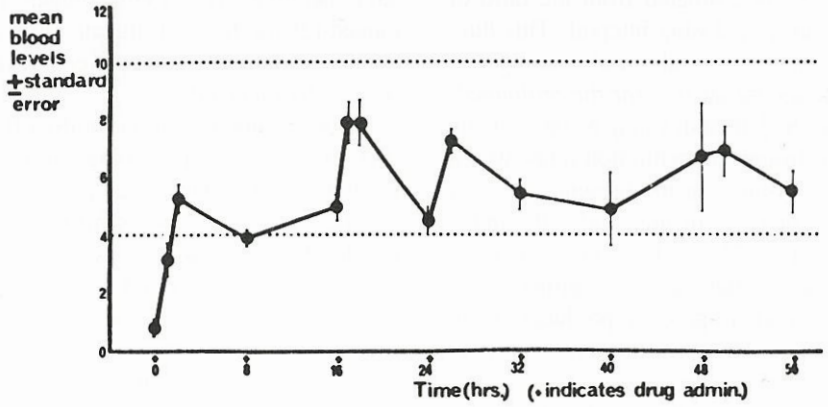

Fig. 7–4. Mean levels of procainamide during repetitive dosing of a prolonged-release tablet every 8 hr. (From Cunningham, T., Sloman, G., and Nyberg, G.[27])

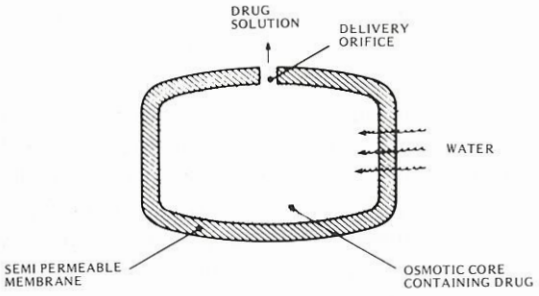

Fig. 7–5. Cross section of an elementary osmotic pump (EOP) designed to release drug in a zero-order (constant-rate) manner. (From Theeuwes, F.[33] Reproduced with permission of the copyright owner.)

On the other hand, the slower the release of lithium from a dosage form, the higher is the incidence of diarrhea. This adverse effect seems to be related to high concentrations of lithium in the distal intestine, a situation found only with prolonged-release products.[31] More recent studies confirm these results.[32]

Zero-Order Release

The ideal approach to minimizing blood level fluctuations of a drug is to have zero-order release from the dosage form. A system, termed the elementary osmotic pump (EOP), is now available to achieve this goal. Figure 7–5 shows a diagram of this dosage form, which resembles a coated tablet. The EOP tablet contains a solid core of drug and adjuvants coated with a polymer membrane, permeable to water and interrupted only by a single small orifice with a diameter of 0.1 to 0.4 mm.[33] After the tablet is swallowed, the membrane selectively admits water from the gastrointestinal tract; drug within the membrane is gradually dissolved. The internal pressure produced by entry of the water forces the drug solution out of the orifice. Since the volume of the system is fixed, constant-rate release is achieved. Typically, 60 to 80% of drug content is delivered at a constant rate; the rest of the dose is released in a pseudo-first-order fashion. The depleted membrane sac is excreted intact. Release rates as high as 60 mg/hr may be achieved with this dosage form. Drug release is independent of pH or motility.

The duration of drug delivery is controlled by the permeability of the membrane and the composition of the core. At a given rate of drug delivery, the duration of controlled release is determined by the amount of drug in the core. In practice, however, the duration of release is limited by intestinal transit time and probably cannot exceed 8 to 12 hr without compromising the extent of absorption.

The hemodynamic effects and plasma levels of metoprolol have been determined after single and multiple doses of EOP tablets or more conventional prolonged-release tablets of the drug.[37] Both dosage forms were given once a day for 8 days to healthy subjects. The prolonged-release tablets contained 200 mg metoprolol tartrate; the EOP tablets contained 190-mg metoprolol fumarate (equivalent to 200 mg of the tartrate) with a 19 mg/hr zero-order release rate. Both formulations reduced exercise heart rate and exercise systolic blood pressure for the entire 24-hr steady-state dosing interval, but the EOP tablets elicited a more uniform response. Mean steady-state plasma profiles of me-

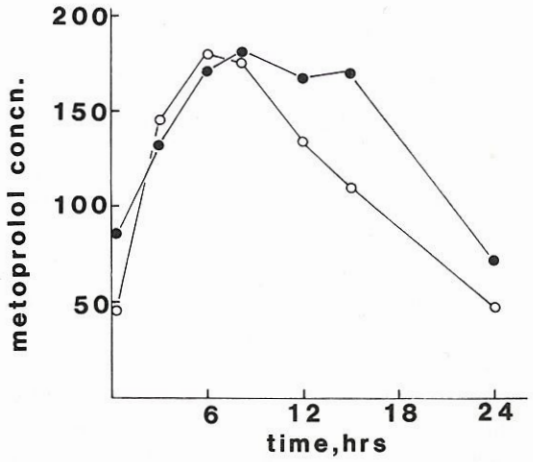

Fig. 7–6. Mean steady-state plasma concentrations of metoprolol (ng/ml) in healthy subjects after repetitive dosing of an EOP prolonged-release product (●) or a more conventional prolonged-release product (○), once a day. (Data from Kendall, M.J., et al.[34])

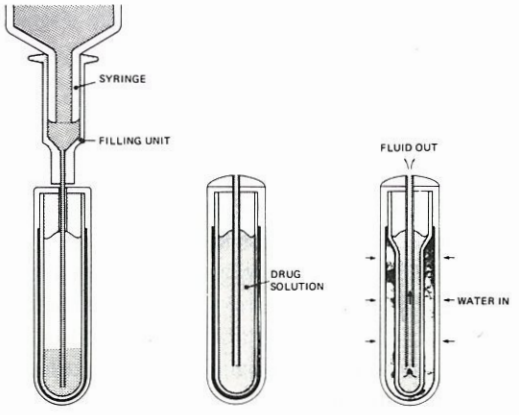

Fig. 7–7. Schematic representation of the filling and operation of the osmotic pump. (From Eckenhoff, B., and Yum, S.I.[38] By permission of the publishers, Butterworth & Co. Ltd. Copyright 1981.)

toprolol are shown in Figure 7–6. Peak-to-trough concentration ratios were 4.5 for the conventional prolonged-release tablets and 2.6 for the EOP tablets. Fluctuation indices were 1.31 for the prolonged-release tablets and 0.88 for the EOP tablets. Both hemodynamic and pharmacokinetic criteria support the superiority of the EOP tablet.

The steady-state metoprolol levels produced by the EOP tablets show considerable fluctuation over the dosing interval even though release rate approximated zero-order. This occurs because release took place over a relatively small fraction (10 out of 24 hr) of the dosing interval. To obtain constant blood levels, there must be constant-rate release over the entire dosing interval. This situation was more closely approximated in studies with acetazolamide, a drug that reduces intraocular pressure, in EOP tablets.[35] Relatively constant blood levels of acetazolamide were obtained by dosing every 12 hr with EOP tablets that release the drug over an 8-hr period, or about three quarters of the dosing interval.

Bayne et al.[36] described the evaluation of constant release rate dosage forms of indomethacin, based on the elementary osmotic pump principle and intended to be taken twice a day. Indomethacin is usually given 3 or 4 times a day in the treatment of rheumatoid arthritis and osteoarthritis.

Steady-state levels of indomethacin were determined in plasma of healthy subjects who had received 150 mg/day for 5 days according to the following regimens: (a) controlled-release tablet delivering drug over 8 hr, given twice a day; (b) controlled-release tablet delivering drug over 11 hr, given twice a day; (c) regular capsules of indomethacin given 4 times a day; (d) regular capsules given 3 times a day.

Average indomethacin levels in plasma at steady state were similar for all four regimens, but subjects taking the prolonged-release dosage forms showed much less fluctuation in plasma levels of drug than subjects taking regular capsules. Also, trough levels of indomethacin before the morning dose were significantly higher during treatment with controlled-release tablets than with regular capsules. This difference may be important for the relief of morning stiffness often seen in arthritics.

Generic osmotic pumps are also available as experimental tools for animal or clinical studies. They are useful for, but not limited to, oral administration.[9,37,38] A diagram of this dosage form is shown in Figure 7–7. The reservoir is filled with a drug solution. The wall of the reservoir is inert, impermeable, and flexible. A sleeve of osmotically active agent is placed between the reservoir wall and the rigid semipermeable membrane.

Water from the surroundings is imbibed through the outer membrane into the osmotic sleeve at a rate controlled by the permeability of the membrane and the osmotic pressure difference across the membrane. The incoming water squeezes the reservoir and drug solution is expelled in a constant-volume per-unit-time fashion. Delivery of

drug solution continues at a constant rate until the drug reservoir is completely collapsed.

Limitations of Prolonged-Release Medication

A factor that circumscribes the use of oral prolonged-release medication is the limited residence time of the dosage form in the small intestine. Absorption from the colon may be poor or unpredictable. Hence, small intestine transit time is often of paramount importance in determining the bioavailability of the drug from this dosage form.

The gastrointestinal transit of a radiolabeled osmotic tablet (elementary osmotic pump) has been monitored in groups of young and elderly healthy human subjects.[39] Gastric emptying and small intestine transit were similar for both groups of subjects. Gastric emptying of the tablet when given after a light breakfast (orange juice, cornflakes, and milk) averaged about 3 hr; the tablets arrived at the cecum, on average, about 7 hr after dosing.

In another study, the position in the gastrointestinal tract of an orally administered osmotic tablet containing a radiolabel and oxprenolol, a beta-blocker available in Europe, was followed in fasted subjects by gamma scintigraphy.[40] Gastric emptying times (about 1 hr) and the time to arrival in the colon (about 4 hr) were relatively consistent from one subject to another.

On the other hand, there were wide individual variations in colonic transit with values ranging from 2.5 to 27.5 hr. Accordingly, total transit time ranged from 6 to 32 hr. In the individual with the most rapid colonic transit and total transit, the bioavailability of oxprenolol was only 14%, and 79% of the administered dose was recovered in the stool. In the two individuals with the slowest colonic transit, bioavailability was 40% and 54%.

External gamma scintigraphy was also used to monitor the gastrointestinal transit of radiolabeled prolonged-release tablets containing 800 mg ibuprofen in fasted healthy subjects.[41] The tablet was formulated using an erodible polymer matrix system.

The gastric retention time of the tablets ranged from 10 to 60 min, with a mean value of 35 min. Transit time of a tablet through the small intestine was calculated by subtracting gastric residence time from the time at which the tablet was observed to enter the large bowel. Small bowel transit time ranged from about 2 to 8 hr, with a mean value of 4.7 hr. Again, total transit time was variable (8 to 18 hr) and largely dependent on large bowel residence time, which ranged from 6 to 14 hr.

A statistically significant correlation ($r = 0.89$) was observed between the area under the curve for 24 hr after administration of ibuprofen and total gastrointestinal transit time. Area under the curve for the subject with the most rapid total transit time (8 hr) was only 94 μg-hr/ml compared with a mean value for the group of 180 μg-hr/ml.

For dosage forms like the matrix tablet or the elementary osmotic pump, which remain intact in the gastrointestinal tract, we usually assume an average effective absorption time of 9 to 12 hr after administration. The release rate of drug from the dosage form must be programmed accordingly. Slower release rates run the risk of poor bioavailability. For dosage forms with similar transit times that release drugs in an apparent first-order manner, release half-lives should not exceed 3 to 4 hr.

Since there is a limit to how much we can reduce the release rate of a drug from certain prolonged-release dosage forms without compromising bioavailability, there is also a limit as to how much we can prolong the duration of drug action by these oral dosage forms. Mathematical simulations of the time course of drug in the blood on multiple dosing of slow-release dosage forms suggest that ordinarily drugs with relatively short half-lives (i.e., less than or equal to 6 hr), and low therapeutic indices (i.e., less than or equal to 3) should be given no less frequently than every 12 hr.[2]

Prolonged-release dosage forms that consist of beads, pellets, or particulates, or that disintegrate into particulates, may be retained in the small intestine for longer periods. The small intestine transit time of pellets depends on size, density, and composition. One study found that increasing the density of standardized pellets from 1.0 to 1.6 increased the average transit time from 7 to 25 hr,[42] but these results could not be confirmed.[43]

We still cannot predict the effect of food on the bioavailability of drugs given in prolonged-release dosage forms. Investigators recently studied the effect of food-related changes in gastric emptying on the absorption of procainamide from a nondisintegrating wax-matrix sustained-release tablet. Gastric residence time was greater in fed than in fasted subjects (3.5 vs 1 hr), but food had no effect on the time required to detect procainamide in plasma, on the time to reach peak concentration of procainamide, or on the extent of absorption of procainamide.[44] A standard meal also had little ef-

fect on the absorption of pseudoephedrine from a slow-release capsule formulation based on a system using both ion exchange technology and a wax coating.[45]

The effect of food on drug absorption kinetics may differ markedly from one prolonged-release formulation to another. Theophylline is a case in point. Food has little effect on the absorption profile for theophylline after administration of Theo-Dur, a well-absorbed and widely prescribed slow-release theophylline product.[46] The pediatric version of this product, Theo-Dur Sprinkle, is also completely absorbed in fasting subjects but less than half the dose is absorbed when it is taken after breakfast.[47]

Scandinavian scientists reported the results of a study with children and adults who were given a single dose of a prolonged-release theophylline preparation (Theolair-SR) after an overnight fast and later after a standardized breakfast.[48] Food dramatically reduced the absorption rate of theophylline (see Fig. 7–8), particularly in the children, but it had no effect of the extent of absorption.

About two-thirds of the dose of theophylline is absorbed after administration of Uniphyl, another slow-release product, to fasted subjects, whereas 85% of the dose is absorbed when it is given after a meal.[49] Although there is an increase in bioavailability with food, there is little effect on the rate of absorption of theophylline. Theo-24, a once-a-day theophylline product, is also incompletely absorbed in fasting subjects. With this product, however, food not only increases the extent of absorption, but also greatly increases the rate of absorption with about half the daily dose absorbed in a 4-hr period, giving rise to excessively high blood levels of theophylline.[50]

Exposure of the distal small intestine and colon to drug is far more likely when a prolonged-release formulation rather than a conventional tablet or capsule is taken. In some cases, this may result in a higher incidence of lower bowel toxicity. Microorganisms in the lower bowel may enzymatically reduce a drug, leading to metabolites that are not ordinarily seen after administration of the drug in conventional dosage forms. Bacterial metabolism may decrease bioavailability or result in toxic metabolites.

Drugs that are metabolized and inactivated by the gastrointestinal mucosa during absorption may show a higher availability after administration in conventional dosage forms than in slow-release forms, because of capacity-limited biotransformation. This may explain why the apparent bioavailability of chlorpromazine in man is significantly less after administration of a prolonged-release capsule than after administration of a liquid or tablet dosage form of the drug.[49]

Drugs that are efficiently absorbed only in the proximal intestine should not be administered in a prolonged-release product. The consequence of this approach would be incomplete absorption.

PARENTERAL MEDICATION

Intramuscular Injections

There has been interest for many years in using the slow absorption of insoluble material in a muscle depot as a means of attaining prolonged drug

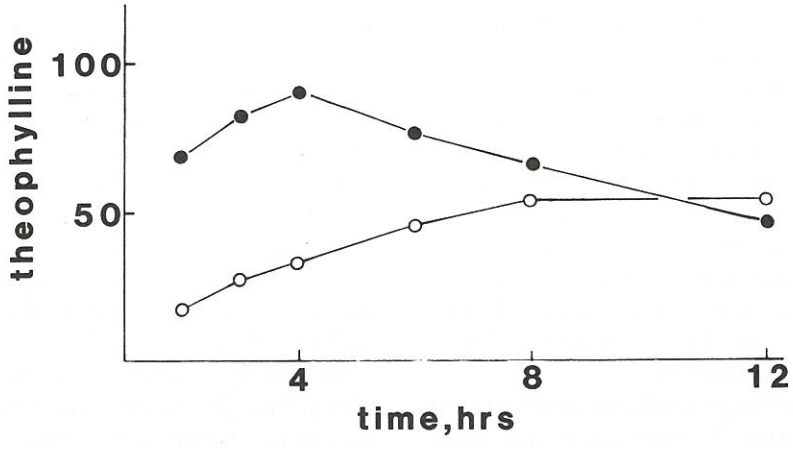

Fig. 7–8. Theophylline concentrations in serum (μmol/L) after a single dose of a prolonged-release product to fasted (●) and fed (○) children. (Data from Pedersen, S.[48])

action. Unlike oral prolonged-release dosage forms, parenteral therapy is not restricted in frequency of administration to once or twice a day. Therefore, these dosage forms can be administered weekly, monthly, or even less frequently. Sterile aqueous suspensions of insoluble salts of penicillin G, such as procaine penicillin G and benzanthine penicillin G, are available for intramuscular injection. These preparations are administered less frequently than injectable solutions of potassium penicillin G. Another long-acting intramuscular penicillin preparation consists of procaine penicillin G suspended in peanut or sesame oil, thickened with aluminum monostearate. Poorly water-soluble esters of prednisolone, testosterone, estradiol, medroxyprogesterone, and fluphenazine are also given as intramuscular injections in the form of aqueous suspensions.

Desoxycorticosterone (DOC) is a mineralocorticoid used as replacement therapy in chronic primary adrenocortical insufficiency. Therapy is initiated with intramuscular DOC acetate (DOCA). Once the maintenance dosage is established, a long-acting, microcrystalline, aqueous suspension of DOC pivalate may be used. The usual intramuscular dose of the pivalate is 25 mg for each mg of the daily maintenance dose of DOCA, repeated at 4-week intervals.

Dexamethasone is a fluorinated derivative of prednisolone used primarily in inflammatory or allergic conditions. Dexamethasone acetate is available as a long-acting repository suspension for intramuscular injection. Long-acting intramuscular formulations of methylprednisolone acetate, prednisolone acetate, triamcinolone acetonide, and triamcinolone diacetate are also available.

Androgens are used for replacement therapy in hormone-deficiency states in men and for certain gynecologic conditions and metastatic breast cancer in women. Androgens or anabolic steroids are also used in certain cases to increase growth.

Testosterone itself is not suitable for therapeutic use, except perhaps topically or by means of subcutaneous implants, because it is subject to rapid hepatic metabolism. This problem is overcome by using testosterone esters that are hydrolyzed to testosterone in the body. The esters are dissolved in oil and injected intramuscularly.

In general, the longer the hydrocarbon chain of the ester substituent, the more slowly is testosterone released into the systemic circulation. The most common esters of testosterone are the propionate, cypionate, and enanthate. Testosterone propionate is usually injected several times a week, but the longer-acting cypionate and enanthate esters need be given every 2 to 4 weeks. These longer-acting esters are drugs of choice for hypogonadism, which requires long-term therapy.

A slow-release intramuscular preparation of a luteinizing-hormone releasing-hormone (LHRH) agonist, formulated in microcapsules designed to release 100 μg/day, has also been described.[52] This preparation, administered once a month, was effective in patients with advanced ovarian and advanced prostatic carcinoma.

Failure to take medication frequently complicates the management of chronic schizophrenia. Fluphenazine decanoate and enanthate are injectable phenothiazine esters that can be administered at intervals of 1 to 3 weeks or longer for treatment of schizophrenia. In contrast, fluphenazine hydrochloride is given orally, 1 to 4 times a day. These poorly water soluble esters are prodrugs and are converted to fluphenazine upon dissolution in the body. The times required, after intramuscular injection in the dog, for 50% of the dose to be excreted in the urine and feces is 7.8 days for the enanthate ester and 22.6 days for the decanoate ester.[53] Dogs were protected against the emetic effects of a 40 μg/kg iv dose of apomorphine for 46 days after being given fluphenazine enanthate and for 105 days after a single dose of the decanoate.[53] Studies in human subjects indicate that absorption from the muscle depot occurs with a half-life of about 3 to 4 days for the decanoate ester.[54] Clinical studies with fluphenazine decanoate indicate that long-acting antipsychotic medication significantly reduces the tendency of chronic psychotic patients to discontinue treatment.[55]

The usual practice of giving fluphenazine decanoate every 2 weeks is primarily based on custom; several lines of evidence suggest that it may be given less frequently. Investigators have studied the persistence of fluphenazine levels in plasma in patients stabilized for at least 1 year on fluphenazine decanoate, 12.5 mg intramuscularly every 2 weeks.[56] Patients were randomized to either continued treatment or placebo injections every 2 weeks for 12 weeks.

No patient relapsed during the study. Mean plasma fluphenazine at baseline for all subjects was 0.86 ng/ml. For the first 6 weeks after withdrawal of the depot medication there was no statistically significant difference in fluphenazine levels be-

tween the continued treatment and placebo groups. The investigators suggested that 2-week intervals between injections of fluphenazine decanoate are excessive and that wider intervals (e.g., 3 to 4 weeks) may achieve similar clinical results.

Haloperidol decanoate, a depot form of the most widely used antipsychotic drug, is also available. The preparation is a sesame oil solution containing the equivalent of 50 mg haloperidol per ml. It is administered by deep injection into the gluteus muscle, usually at monthly intervals. After injection there is slow transfer of the ester from the lipid carrier to the aqueous medium of the tissue. Esterases in muscle tissue and plasma split the ester, releasing haloperidol.

The apparent half-life of haloperidol after depot injection is about 3 weeks. Half-life in this case reflects the release rate of the drug from the muscle depot rather than the rate of metabolism of haloperidol. Steady state occurs after 3 to 4 months of treatment. Short periods of oral haloperidol supplementation may be needed to treat reemergent psychotic symptoms until steady state is reached.

Haloperidol decanoate is intended to be used in patients stabilized on oral haloperidol. An important issue is the relationship between the intramuscular dose and the daily oral dose. As with all neuroleptics, the lowest effective dose is sought to avoid extrapyramidal side effects.

After oral administration, haloperidol is subject to first-pass metabolism; bioavailability is estimated at 60 to 70%. The bioavailability of the intramuscular depot form is probably complete. Based on relative bioavailability and frequency of dosing, a 20-fold conversion is appropriate when switching from oral haloperidol (daily dose) to haloperidol decanoate (dosed every 28 days). Clinical studies suggest that the depot form of the drug may allow even greater dose sparing.[57]

Patients with chronic schizophrenia, stabilized on oral halperidol, were switched to haloperidol decanoate, administered every 4 weeks. The first dose was determined by psychiatric history and the oral dose of haloperidol needed to stabilize the patient. Thereafter, the patient's dose could be adjusted upward or downward at 4-week intervals. For the 30 patients completing the study, the ratio of haloperidol decanoate to oral haloperidol required to achieve equal efficacy ranged from 10:1 to 15:1, lower than the 20:1 ratio needed to maintain equivalent blood levels of haloperidol. These results suggest that by reducing the variability in blood level of a drug, we may be able to achieve equal efficacy with less drug.

Estrogens and progestins are prescribed to mimic or accentuate the biologic effects of endogenous hormones: to supplement inadequate endogenous production, to correct hormonal imbalance, to reverse an abnormal process, and for contraception. Estradiol is the principal and most biologically potent ovarian estrogenic hormone. It is usually given intramuscularly in the form of an ester (benzoate, cypionate, or valerate) in oil or in an aqueous suspension. Duration of effect varies from several days to several weeks depending on the ester and formulation.

Intramuscular progestin products include a sesame-oil solution of hydroxyprogesterone caproate, used for menstrual disorders (duration of action is about 9 to 17 days), and an aqueous suspension of medroxyprogesterone acetate (MPA), used for endometriosis and injected every 3 months.

Several intramuscular depot preparations are under investigation for use as contraceptives. One preparation that is widely used throughout the world (but not in the U.S.) is depot MPA. The contraceptive use of depot MPA has been controversial for more than a decade. The drug is used in 80 countries and its use in developing nations is endorsed by scientific panels of the World Health Organization and other international agencies. The U.S. Food and Drug Administration has repeatedly denied approval of a 3-month depot MPA product for use as a contraceptive, concluding that the potential adverse effects (carcinogenicity and teratogenicity) of the drug outweigh its benefits.

Another depot progestin, norethindrone enanthate, is also used outside the U.S. for contraceptive purposes. An injection schedule calling for the first four injections to be given at 8-week intervals and subsequent injections to be given at 12-week intervals produced no pregnancies in 295 women over about 1,600 women months.[58]

Implants

The technology supporting the use of drug implants is well established but commercially successful clinical applications have been slow in coming. Numerous devices have been described for the diffusion of steroids through silicone rubber. For example, contraceptive devices in the form of silicone-rubber capsules containing progesterone have been implanted subcutaneously. Silicone-rubber capsules containing ethinyl estradiol have

been used in the treatment of patients with prostate cancer. Certain disorders of male reproductive function can be treated with long-acting implants of testosterone.

Many investigators are now applying the principles of prolonged release from silicone rubber and other polymers for long-term drug treatment. Examples include systems for narcotic antagonists, such as naloxone, in the treatment of opiate addiction, chemotherapeutic agents for the treatment of cancer, and heparin in the treatment of abnormal blood clotting.

A subdermal silastic implant containing levonorgestrel has been described. The capsules are implanted into a woman's upper or lower arm with a hypodermic needle. Within 24 hr, enough drug is released from the invisible yet palpable implant to prevent pregnancy. The capsules are said to be effective for 5 years. They can be removed if the woman wishes to become pregnant.

The generic osmotic pump, described earlier in this chapter, is a particularly useful implant for experimental drug studies in animals. The device can be implanted in the subcutaneous tissue, muscle, or peritoneal cavity. A catheter can be attached for localized administration to areas remote from the site of implantation. Commercially available pumps permit constant-rate drug delivery over 1 or 2 weeks. Publications to date have illustrated the use of the generic osmotic pumps for delivering many drugs and chemicals in various animals including mice, rats, rabbits, dogs, monkeys, sheep, and cows.[9]

Refillable implants have also been described.[59] These devices have been used in patients prone to thrombophlebitis and pulmonary embolism who require heparin. Ordinarily, heparin is given to outpatients by subcutaneous injection 4 to 6 times a day. One refillable implant delivers heparin solution continuously over 45 days before refilling is necessary. These implants have also been used to provide an intra-arterial infusion of 5-fluorouracil for the treatment of hepatoma and primary liver cancer. Recent reports describe refillable implants for the delivery of insulin[60] and antiarrhythmic drugs.[61]

A patient with refractory congestive heart failure was treated, on an outpatient basis, with intermittent dobutamine using a totally implantable infusion pump. Dobutamine was infused for 48 hr every week and resulted in sustained clinical improvement.[62]

The Food and Drug Administration has approved the use of an implantable pump to deliver the aminoglycoside antibiotic amikacin directly to the site of an osteomyelitis infection.

Battery-powered pumps were implanted in patients for phase I and II trials of low-dose continuous-infusion doxorubicin or vinblastine. The median duration of pump function was 145 days. The systems infused drugs for about 60% of their patient implant time. During 27.5 patient-years of implantation, no failure of pump mechanism was observed and pump accuracy was within 2% of stated standards. Complications requiring a second surgical procedure occurred in 24% of the patients.[63]

Remote-controlled insulin pumps were implanted into insulin dependent type I diabetics for a 1-year feasibility trial in four centers.[64] The total observation time was about 18 patient-years. Only 3 of 20 pumps had to be removed prematurely. Patients self-monitored blood glucose levels with a mean of 5.5 measurements per day. About 63% of these measurements were in the normal range. On the average, 3.25 glucose measurements per patient-month were in the hypoglycemic range and 2.6 episodes of hypoglycemia with symptoms were reported per patient-month, but very few of these episodes required medical attention. The investigators concluded that despite some technical and clinical problems, the pump, when used with a stable insulin preparation, was an effective means of treating insulin-dependent patients.

OCULAR MEDICATION

Drug effects in the eye tend to be short-lived because of the eye's efficient mechanisms to maintain homeostasis. Ocular inserts intended to release drug slowly, in a controlled fashion, offer the potential benefits of a dramatic decrease in the frequency of dosing, more uniform clinical response, and a decrease in adverse effects.

One device, called the Ocusert, containing pilocarpine, is used for lowering elevated ocular pressure. The patient places the insert under the eyelid, where it remains for 7 days, slowly and continuously delivering pilocarpine. In contrast, pilocarpine eye drops are usually instilled 3 or 4 times daily; high concentrations of the drug after dosing may produce blurring or dimming of vision for as long as 1 hr.

The Ocusert consists of the drug enclosed by a dense membrane. The detailed physical chemistry

of this system is described elsewhere.[65] Pilocarpine dissolves in the membrane and diffuses slowly to the eye. The total dosage delivered by a single Ocusert system over its 7-day lifetime is about one eighth of the amount provided by the usual 2% eye drops of pilocarpine.

Studies in the rabbit show that pilocarpine levels in ocular tissue rise and fall within each 6-hr interval between eye drops but remain relatively constant over a 2- to 8-day period with the Ocusert system (Fig. 7–9).[66] Clinical studies comparing pilocarpine eye drops with the Ocusert found comparable reductions in intraocular pressure, but 36 of the 40 patients preferred the Ocusert.[67] Another comparative study concluded that the Ocusert pilocarpine system presents many advantages and is a desirable method of therapy in selected cases of glaucoma.[68] Advantages of the device include therapeutic effectiveness, less effect on accommodation, less miosis, and convenience for the patient. Some disadvantages were the need for instruction and encouragement of the patient, retention difficulties, occasional discomfort, and higher cost.

INTRAUTERINE DEVICES

Intrauterine devices (IUDs) for contraceptive purposes are available in medicated and unmedicated forms. Medicated devices contain a diffusible contraceptive agent and are claimed to provide greater efficacy than an unmedicated device of the same size and design.

A device containing progesterone (Progestasert) releases small quantities of hormone at a uniform rate (65 μg/day) into the endometrial cavity, resulting in glandular atrophy and a chronic decidual reaction that is unfavorable for implantation; progesterone may also directly inhibit sperm. The device requires yearly replacement but devices containing a larger amount of progesterone have been found to produce effective contraception for 2 years or more.[49] Progestasert contains an amount of progesterone equivalent to the progestational agent contained in merely a half a dozen birth control pills. The product clearly illustrates the principle of using controlled-release technology to determine duration of drug effect; progesterone itself has a half-life of less than 1 hour.

TRANSDERMAL MEDICATION

Transdermal medication is intended to be applied to the skin but to elicit systemic effects. Compared to oral drug therapy, transdermal therapy has the potential advantages of avoiding biochemical degradation in the gastrointestinal tract and presystemic metabolism in the gut wall and liver, and of being able to provide long periods of drug action for relatively short-acting drugs.

Certain factors limit the application of rate-controlled transdermal drug delivery. The most im-

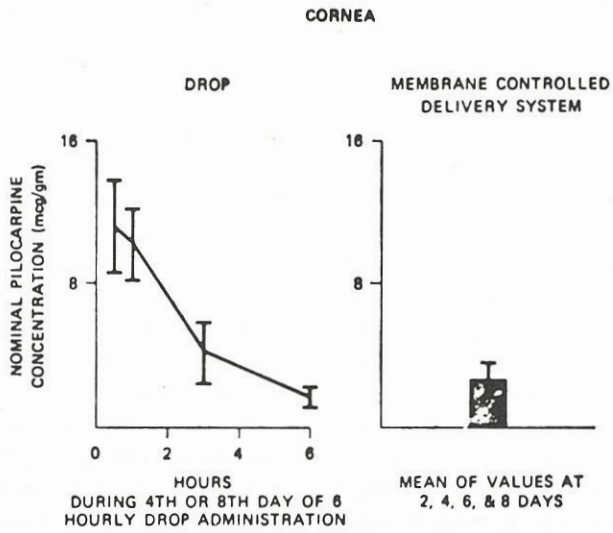

Fig. 7–9. Pilocarpine concentrations in cornea with eye-drop administration of 2% pilocarpine nitrate every 6 hr (left panel) or with a 20 μg/hr membrane-controlled pilocarpine delivery system (right panel). (From Sandelbeck, L., Moore, D., and Urquhart, J.[66] Published with permission from The American Journal of Ophthalmology, *80*:274–283, 1975. Copyright by the Ophthalmic Publishing Company.)

portant one is the need for potent drugs. Existing technology is limited to drugs active at daily parenteral doses of 15 mg or less.

Transdermal scopolamine was the first transdermal system approved in the U.S. with label specifications of rate-controlled delivery. It is indicated for the prevention of motion sickness. The transdermal system is contained in a thin disk that the patient places on intact skin, usually behind the ear. The unit has multiple layers including a backing membrane, a drug reservoir consisting of solid drug suspended in a liquid vehicle, a microporous rate-controlling membrane, and a skin contact adhesive.

Scopolamine is a well-known antiemetic drug; however, it causes undesirable side effects when given in conventional tablets. These side effects appear to be related to the wide fluctuations in scopolamine concentrations in blood that occur between doses. The transdermal scopolamine system is applied only once every 3 days and provides relatively constant blood levels of scopolamine over this period.

The transdermal product delivers 0.5-mg scopolamine over 3 days. A priming quantity of 140 μg of drug is released at an asymptomatically declining rate over 6 hr, stabilizing at a maintenance rate of 5 μg/hr for the remainder of the 3-day period.

Efficacy of transdermal scopolamine has been compared with oral dimenhydrinate and placebo.[70] The transdermal device was applied 13.5 to 15 hr before exposure to motion; oral medication was given 1.5 hr before motion, and again 2.5 hr after motion began. In one study, directly comparing transdermal scopolamine with oral dimenhydrinate, the transdermal medication protected 79% of the subjects from motion sickness, whereas the oral drug protected 58%; in a second study, protection rates of 68% and 41% were found for the scopolamine and dimenhydrinate therapy, respectively. No patient was protected by the placebo.

Another study examined the influence of the time between application and exposure to motion on the efficacy of the transdermal system. Application 16 hr before motion resulted in a 100% protection rate; application 4 hr before motion protected 74% of the participants. Dry mouth, drowsiness, and blurred vision, typical side effects of scopolamine, were minimal with the transdermal system.

Other investigators have found that transdermal scopolamine is significantly more effective in preventing motion sickness induced by a ship-motion simulator than is placebo or orally administered meclizine (25 mg), a commonly used antihistamine/antinauseant.[71] A patch containing either placebo or active drug was applied behind the ear 12 hr before exposure to the simulator, and meclizine or placebo tablet was taken 2 hr before exposure. The trial lasted 90 min or until vomiting was imminent.

About two-thirds of the patients receiving transdermal scopolamine had no symptoms compared with 33% given oral meclizine and 39% given placebo. Dryness of mouth was reported more frequently with scopolamine than with meclizine or placebo. No other side effects were notable. Transdermal scopolamine may be the treatment of choice for motion sickness, but the patch must be applied at least several hours before motion to obtain optimal effect.

Several transdermal nitroglycerin systems have been marketed for the treatment of angina pectoris. These systems are more convenient to use than nitroglycerin ointment, permit more precise dosing, and need be applied less frequently than the ointment. All are intended to be applied to the upper arm or chest once a day. They should not be applied to the distal part of the extremities because bioavailability may be decreased.

Chien et al.[72] applied three commercially available nitroglycerin patches to freshly excised abdominal skin from young hairless mice and determined skin-penetration kinetics. They found that the amount of nitroglycerin delivered through the skin over 24 hr was similar for each transdermal system, ranging from 3.3 to 3.5 mg.

Other investigators measured the bioavailability of nitroglycerin from a reformulated transdermal system (Nitro-Dur II) relative to the original product (Nitro-Dur) in healthy male subjects.[73] The apparent dose of nitroglycerin delivered to each subject by each formulation was calculated from the difference between the original content of the patch and the residual nitroglycerin content after 24 hr of skin contact.

The mean total amounts of nitroglycerin delivered by the original product (I) and Nitro-Dur II were similar, 9.8 mg and 10.7 mg, respectively. Large differences in delivery, however, were observed in individual subjects; only 2.5 mg nitroglycerin was delivered from the original formulation in one subject, whereas in another subject the same formulation delivered 19.3 mg. The new for-

mulation in the same two subjects delivered 7.4 and 14.4 mg nitroglycerin, respectively. Transport through the skin rather than release from the dosage form is the rate-limiting step in the transdermal absorption of nitroglycerin. Differences among subjects reflect differences in skin permeability.

Transdermal nitroglycerin was conditionally approved by the Food and Drug Administration for the prevention and treatment of angina pectoris due to coronary artery disease. Blood level measurements demonstrating nitroglycerin concentrations in plasma similar to concentrations produced by nitroglycerin ointment, a product with established efficacy, was largely the basis for approval. According to the FDA, conditional approval reflects a determination that the drug may be marketed, while further investigations of its effectiveness are undertaken. At this time, the FDA has not made a final determination.

The evidence to date suggests rather serious shortcomings of the once-a-day nitroglycerin patch mostly related to nitrate tolerance, a well-known phenomenon. Many studies using transdermal nitroglycerin in patients with angina or congestive heart failure that have demonstrated effectiveness within several hours of application of the transdermal system, have also documented the attenuation or absence of effects within 12 to 24 hr. Other studies have suggested that complete tolerance may develop in a short time during continuous once-a-day administration of a nitroglycerin patch.[74]

A comprehensive analysis of the published clinical literature on transdermal nitroglycerin systems for the treatment of angina concluded that the patch delivering 10 mg per 24 hr is not effective at 24 hr after application.[75] This conclusion supports the hypothesis that nitroglycerin's effect on exercise tolerance is attenuated by nitrate tolerance even though blood levels persist.

A randomized controlled trial in more than 400 men with chronic stable angina showed that continuous use of transdermal nitroglycerin 5 mg/24 hr had no advantage over placebo in terms of efficacy (anginal attack rates and sublingual nitroglycerin consumption) or quality of life (as measured by a sickness impact profile and a health index of disability).[76] Patients receiving nitroglycerin reported headaches more frequently than patients on placebo and a higher proportion of them withdrew from the trial for this reason.

The future of transdermal nitroglycerin is uncertain. Current trends suggest that the dosage form will continue to be used but in doses of 10 mg/24 hr or higher, applied intermittently with a nitrate-free period (e.g., 12 hr on, 12 hr off) rather than continuously. A rest period between applications may restore sensitivity and overcome tolerance. Several studies have produced results supporting this hypothesis.[74]

Clonidine is an effective centrally-acting antihypertensive drug, but oral therapy requires administration 2 to 4 times a day and is associated with a relatively high incidence of adverse effects. Transdermal clonidine was developed with the aim of reducing frequency of administration to once weekly and with the hope of reducing side effects.

One multicenter trial evaluated weekly application of transdermal clonidine patches in patients with mild essential hypertension (diastolic blood pressure in the range of 91 to 104 mm Hg).[77] Of the 85 patients completing the trial, 54 responded (diastolic pressure $<$ 90 mm Hg or a decrease in diastolic pressure of at least 10 mm Hg). Among the responders, 31% required one patch (releasing clonidine at a rate of 0.1 mg/day), 54% required two patches, and the other 19% needed three.

Dry mouth and drowsiness, typical side effects of clonidine, occurred in about one-third of the patients, but these symptoms were usually mild and only two subjects had to be dropped because of side effects. Of far greater concern, erythematous skin reactions were observed in 8 patients. This report and others suggest a frequency of skin reactions considerably higher than that encountered with oral clonidine. This problem may limit the use of transdermal clonidine.[78]

Most postmenopausal women who require estrogen-replacement therapy use oral medication. With this approach, however, the liver is exposed to relatively high concentrations of estrogen; increased production of coagulation factors, renin substrate, and bile acids may occur. These changes may account for the increased incidence of venous thrombosis and pulmonary embolism, hypertension, and gallstones in women treated with estrogens. This concern stimulated interest in the administration of estrogens in a way that minimizes hepatic exposure and led to the development of transdermal estradiol.

A patch releasing either 50 or 100 μg estradiol per day was approved in the U.S. for the treatment of postmenopausal symptoms but not for the prevention of osteoporosis. Transdermal estradiol may

be useful in this regard but the evidence is not yet available. The advantages claimed for the patch over oral estrogens are that estradiol goes directly to the blood (avoiding gastrointestinal effects, first-pass hepatic metabolism, and stimulation of hepatic enzymes), doses are much lower, and serum concentrations more closely resemble those found naturally before menopause.[79]

The dosage unit consists of a drug reservoir, a rate-controlling membrane, and an adhesive layer. It is intended to be applied to the trunk (but not the breasts) twice weekly. Like other estrogens for postmenopausal symptoms, the patches are generally used in cycles such as 3 weeks on and 1 week off and require the additional administration of a progestin to reduce the risk of endometrial hyperplasia and subsequent complications.

Transdermal estradiol appears to be as effective as much higher doses of oral estrogen in treating postmenopausal vasomotor symptoms, but whether the patches will be safer remains to be determined. The most common adverse effect observed with transdermal therapy has been mild to moderate erythema at the application site. This may be related to the formulation rather than to the drug itself because the problem occurs with both active and placebo patches.

BUCCAL MEDICATION

A transmucosal controlled-release formulation, containing 1, 2, or 3 mg of nitroglycerin, is available in the U.S. for both acute treatment and long-term control of angina pectoris. The product contains nitroglycerin impregnated in an inert cellulose polymer matrix. When the tablet is placed in the buccal cavity between the upper lip and gum, or between the cheek and gum, a gel forms that makes the tablet adhere to the mucosal surface, and drug slowly diffuses from the formulation to saliva and across the mucosal membranes to the systemic circulation.[80]

Onset of effects occurs in minutes and nitroglycerin continues to be absorbed as long as the tablet remains intact, usually about 4 to 5 hours. Treadmill studies in patients with angina found beneficial effects for up to 5 hours when the tablet remained intact for 5 to 6 hours. If continuous nitroglycerin therapy is desired, the next tablet should be taken within 1 hour after the previous tablet dissolves. Tolerance has not been reported with up to 2 weeks' use of transmucosal nitroglycerin, possibly because intermittent use produces a rapid rise and fall in plasma and tissue nitroglycerin levels with a nitrate-free interval at night when no medication is taken.[80]

The analgesic effects of buccal and intramuscular morphine were compared in patients who experienced pain after elective orthopedic surgery.[81] Each patient simultaneously received a buccal tablet and an injection, only one of which contained morphine. Tablets were moistened, to facilitate adherence to the mucosa, and placed between the upper lip and gum. They dissolved slowly, over about 6 hr. Efficacy was evaluated over an 8-hr period.

Seven of the 20 patients given buccal morphine required a second dose within 8 hours of the first dose; 10 of the 20 patients receiving intramuscular morphine required a second dose. As judged by the reduction in pain score, both preparations produced a similar degree of postoperative analgesia. Concentrations of morphine in plasma were lower after buccal morphine but persisted for a longer time than morphine levels after injection. The investigators suggested that this may be a useful dosage form in the management of postoperative pain.

RECTAL MEDICATION

No prolonged-release rectal dosage forms are commercially available. The generic osmotic pump, described earlier in this chapter, however, has been administered rectally in several pharmacokinetic studies in human subjects.

In one study,[82] healthy subjects inserted an osmotic pump containing antipyrine. The system remained in place in the lower rectum with a small thread attached to it and fixed to the buttock, unless there was a need to defecate. In this case, the system was pulled out, cleaned, and reinserted immediately after defecation. After 38 hr, the first system was replaced by a second which stayed in the rectum for an additional 60 hr. The constant-release rate from the osmotic pump gave rise to constant blood levels of antipyrine over a 24- to 90-hr period. This approach may be an alternative to constant rate intravenous infusion for steady state studies.

The effects of relatively constant plasma levels of triazolam, a rapidly eliminated benzodiazepine, were studied in young healthy male subjects to determine whether tolerance to certain effects may develop over a relatively short period of time.[83] The drug was given over a period of 30 hr (2 days

and 1 night) at a zero-order rate using a rectal osmotic pump. The investigators concluded that the experimental design might prove useful in the study of tolerance to drugs.

The utility of an osmotic rectal drug delivery system as a tool in steady-state pharmacokinetic interaction studies has been investigated using the cimetidine-antipyrine interaction.[84] Antipyrine was given by means of a rectal osmotic pump releasing the drug at a zero-order rate of 15 mg/hr for about 30 hr. By consecutive use of three of these systems, antipyrine was administered for 90 hr. Forty-eight hr after the start of the study, when steady state had been achieved, 400 mg cimetidine was given orally followed by three consecutive 200-mg cimetidine doses every 2 hr. The investigators concluded that the osmotic rectal drug delivery system is a useful tool in pharmacokinetic interaction studies because it provides constant steady-state concentrations, permitting investigation of the time course of drug interactions.

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