Clinical Pharmacokinetics

Concepts and Applications

third edition

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Accurate indications, adverse reactions, and dosage schedules for drugs are provided in this book, but it is possible they may change. The reader is urged to review the package information data of the manufacturers of the medications mentioned.

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WHY CLINICAL PHARMACOKINETICS?

Those patients who suffer from chronic ailments such as diabetes and epilepsy may have to take drugs every day for the rest of their lives. At the other extreme are those who take a single dose of a drug to relieve an occasional headache. The duration of drug therapy is usually between these extremes. The manner in which a drug is taken is called a *dosage regimen*. Both the duration of drug therapy and the dosage regimen depend on the therapeutic objectives, which may be either the cure, the mitigation, or the prevention of disease. Because all drugs exhibit undesirable effects, such as drowsiness, dryness of the mouth, gastrointestinal irritation, nausea, and hypotension, successful drug therapy is achieved by optimally balancing the desirable and the undesirable effects. To achieve optimal therapy, the appropriate "drug of choice" must be selected. This decision implies an accurate diagnosis of the disease, a knowledge of the clinical state of the patient, and a sound understanding of the pharmacotherapeutic management of the disease. Then the questions How much? How often? and How long? must be answered. The question How much? recognizes that the magnitudes of the therapeutic and toxic responses are functions of the dose given. The question How often? recognizes the importance of time, in that the magnitude of the effect eventually declines with time following a single dose of drug. The question How long? recognizes that a cost (in terms of side effects, toxicity, economics) is incurred with continuous drug administration. In practice, these questions cannot be divorced from one another. For example, the convenience of giving a larger dose less frequently may be more than offset by an increased incidence of toxicity.

In the past, the answers to many important therapeutic questions were obtained by trial and error. The dose, interval between doses, and route of administration were selected, and the patient's progress followed. The desired effect and any signs of toxicity were carefully noted, and if necessary, the dosage regimen was adjusted empirically until an acceptable balance between the desired effect and toxicity was achieved. Eventually, after considerable experimentation on a large number of patients, reasonable dosage regimens were established (Table 1–1), but not without some regimens producing excessive toxicity or proving ineffective. Moreover, the above empirical approach left many questions unanswered. Why, for example, does tetracycline have to be given every 6 to 8 hours to be effective, while digoxin can be given once daily? Why must oxytocin be infused intravenously? Why is morphine more effective given intramuscularly than when given orally? Furthermore, this empirical approach contributes little, if anything, toward establishing a safe, effective dosage regimen of another drug. That is, our basic understanding of drugs has not been increased.

To overcome some of the limitations of the empirical approach and to answer some of the questions raised, it is necessary to delve further into the events that follow drug administration. *In vitro* and *in vivo* studies show that the magnitude of the response is a function of the concentration of drug in the fluid bathing the site(s) of action. From these observations the suggestion might be made that the therapeutic objective can be achieved by maintaining an adequate concentration of drug at the site(s) of action for the duration

of therapy. However, rarely is a drug placed at its site of action. Indeed, most drugs are given orally, and yet they act in the brain, on the heart, at the neuromuscular junction, or elsewhere. A drug must therefore move from the site of administration to the site of action. Simultaneously, however, the drug distributes to all other tissues including those organs, notably the liver and the kidneys, that eliminate it from the body.

Figure 1–1 illustrates the events occurring after a dose of drug is administered orally. The rate at which drug initially enters the body exceeds its rate of elimination; the concentrations of drug in blood and other tissues rise, often sufficiently high to elicit the desired therapeutic effects and sometimes even to produce toxicity. Eventually, the rate of drug elimination exceeds the rate of its absorption, and thereafter, the concentration of drug in both blood and tissues declines and the effect(s) subsides. To administer drugs optimally, therefore, knowledge is needed not only of the mechanisms of drug absorption, distribution, and elimination but also of the kinetics of these processes, that is, *pharmacokinetics*. The application of pharmacokinetic principles to the therapeutic management of patients is *clinical pharmacokinetics*.

Table 1–1. Empirically Derived Usual Adult Dosage Regimens of Some Representative Drugs *Before* the Introduction of Clinical Pharmacokinetics[a]

DRUG	INDICATED USE	ROUTE	DOSAGE REGIMEN
Tetracycline	Treatment of Infections	Oral	250 mg every 6–8 hr
Digoxin	Amelioration of congestive cardiac failure	Oral	1.5–2 mg initially over 24 hr, thereafter 0.25–0.5 mg once a day
Oxytocin	Induction and maintenance of labor	Intravenous	0.2–4 milliunits/min by infusion
Morphine sulfate	Relief of severe pain	Intramuscular	10 mg when needed
		Oral	Not recommended because of reduced effectiveness

[a]Taken from American Medical Association: Drug Evaluations. 2nd Ed., Publishers Science Group, Acton, MA, 1973.

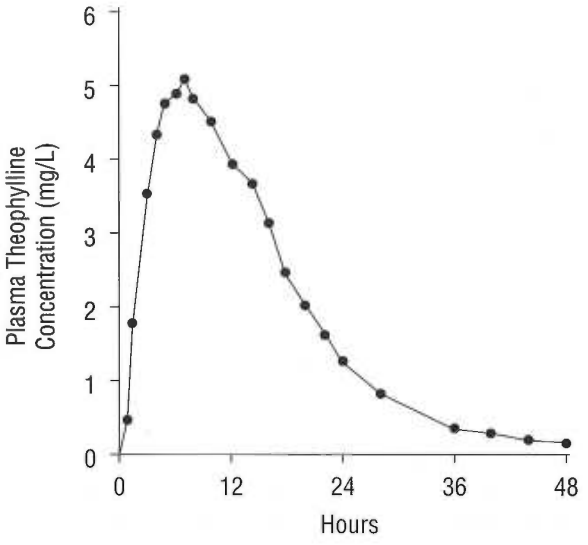

Fig. 1–1. Plasma concentration of theophylline in a subject following an oral dose of a 600-mg controlled-release formulation. Before the peak is reached, the rate of absorption exceeds that of elimination. At the peak, the two rates are equal; thereafter, the rate of elimination exceeds that of absorption. (Redrawn from Sauter, R., Steinijans, V.W., Diletti, E., Böhm, A., and Schulz, H.U.: Presentation of results in bioequivalence studies. Int. J. Clin. Pharmacol. Ther. Toxicol., *30*:S7–30, 1992.)

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The events following drug administration can be divided into two phases, a *pharmacokinetic phase*, in which the adjustable elements of dose, dosage form, frequency, and route of administration are related to drug level–time relationships in the body, and a *pharmacodynamic phase*, in which the concentration of drug at the site(s) of action is related to the magnitude of the effect(s) produced (Fig. 1–2). Once both of these phases have been defined, a dosage regimen can be designed to achieve the therapeutic objective. Despite the greater amount of information required with this approach, it has several advantages over the empirical approach. First, and most obvious, distinction can be made between pharmacokinetic and pharmacodynamic causes of an unusual drug response. Second, the basic concepts of pharmacokinetics are common to all drugs; information gained about the pharmacokinetics of one drug can help in anticipating the pharmacokinetics of another. Third, understanding the pharmacokinetics of a drug often explains the manner of its use; occasionally such an understanding has saved a drug that otherwise may have been discarded or has suggested a more appropriate dosage regimen. Lastly, knowing the pharmacokinetics of a drug aids the clinician in anticipating the optimal dosage regimen for an individual patient and in predicting what may happen when a dosage regimen is changed.

A basic tenet of clinical pharmacokinetics is that the magnitudes of both the desired response and toxicity are functions of the drug concentration at the site(s) of action. Accordingly, therapeutic failure results when either the concentration is too low, giving ineffective therapy, or is too high, producing unacceptable toxicity. Between these limits of concentration lies a region associated with therapeutic success; this region may be regarded as a "therapeutic window." Rarely can the concentration of the drug at the site of action be measured directly; instead the concentration is measured at an alternative and more accessible site, *the plasma*.

Based on the foregoing considerations, an optimal dosage regimen might be defined as one that maintains the plasma concentration of a drug within the therapeutic window. For many drugs, this therapeutic objective is met by giving an initial dose to achieve a plasma concentration within the therapeutic window and then maintaining this concentration by replacing the amount of drug lost with time. One popular and convenient means of maintenance is to give a dose at discrete time intervals. Figure 1–3 illustrates the basic features associated with this approach by depicting the concentrations that follow the administration of two regimens, A and B. The dosing interval is the same but the dose given in regimen B is twice that given in regimen A. Because some drug always remains in the body from preceding doses, accumulation occurs until, within a dosing interval, the amount lost equals the dose given; a characteristic saw-toothed plateau is then achieved. With regimen A,

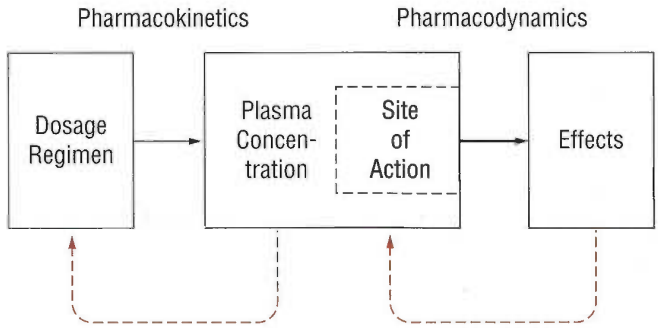

Fig. 1–2. An approach to the design of a dosage regimen. The pharmacokinetics and the pharmacodynamics of the drug are first defined. Then, either the plasma drug concentration-time data or the effects produced are used via pharmacokinetics as a feedback (dashed lines) to modify the dosage regimen to achieve optimal therapy.

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