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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OBJECTIVES

The reader will be able to:

1. Predict the rate and extent of drug accumulation for a given regimen of fixed dose and fixed interval.
2. Develop a dosage regimen from knowledge of the pharmacokinetics and therapeutic window of a drug.
3. Evaluate the kinetics of a drug given in a multiple-dose regimen.
4. Evaluate the kinetics of a drug following a multiple-dose regimen of a controlled-release formulation.
5. Derive pharmacokinetic parameters for a drug from plasma concentration (or urine) data following a multiple-dose regimen.

The previous chapter dealt with constant-rate regimens. Although these regimens possess many desirable features, they are not the most common ones. The more common approach to the maintenance of continuous therapy is to give multiple discrete doses. This chapter covers the pharmacokinetic principles associated with such multiple-dose regimens.

DRUG ACCUMULATION

Drugs are most commonly prescribed to be taken on a fixed dose, fixed time interval basis; e.g., 100 mg three times a day. In association with this kind of administration, the plasma concentration and amount in the body fluctuate and, similar to an infusion, rise toward a plateau.

Consider the simplest situation of a dosage regimen composed of equal bolus doses administered intravenously at fixed and equal time intervals. Curve A of Fig. 7–1 shows how amount in the body varies with time when each dose is given successively twice every half-life. Under these conditions drug accumulates substantially. Accumulation occurs because drug from previous doses has not been completely removed.

Maxima and Minima on Accumulation to the Plateau

To appreciate the phenomenon of accumulation, consider what happens when a 100-mg bolus dose is given intravenously every elimination half-life. The amounts in the body just after each dose and just before the next dose can readily be calculated; these values correspond to the maximum (A_{max}) and minimum (A_{min}) amounts obtained within each dosing interval. The corresponding values during the first dosing interval are 100 mg ($A_{1,max}$) and 50 mg ($A_{1,min}$), respectively. The maximum amount of drug in the second dosing interval ($A_{2,max}$), 150 mg, is the dose (100 mg) plus the amount remaining from the previous dose

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