# CLINICAL PHARMACOKINETICS AND PHARMACODYNAMICS

## CONCEPTS AND APPLICATIONS

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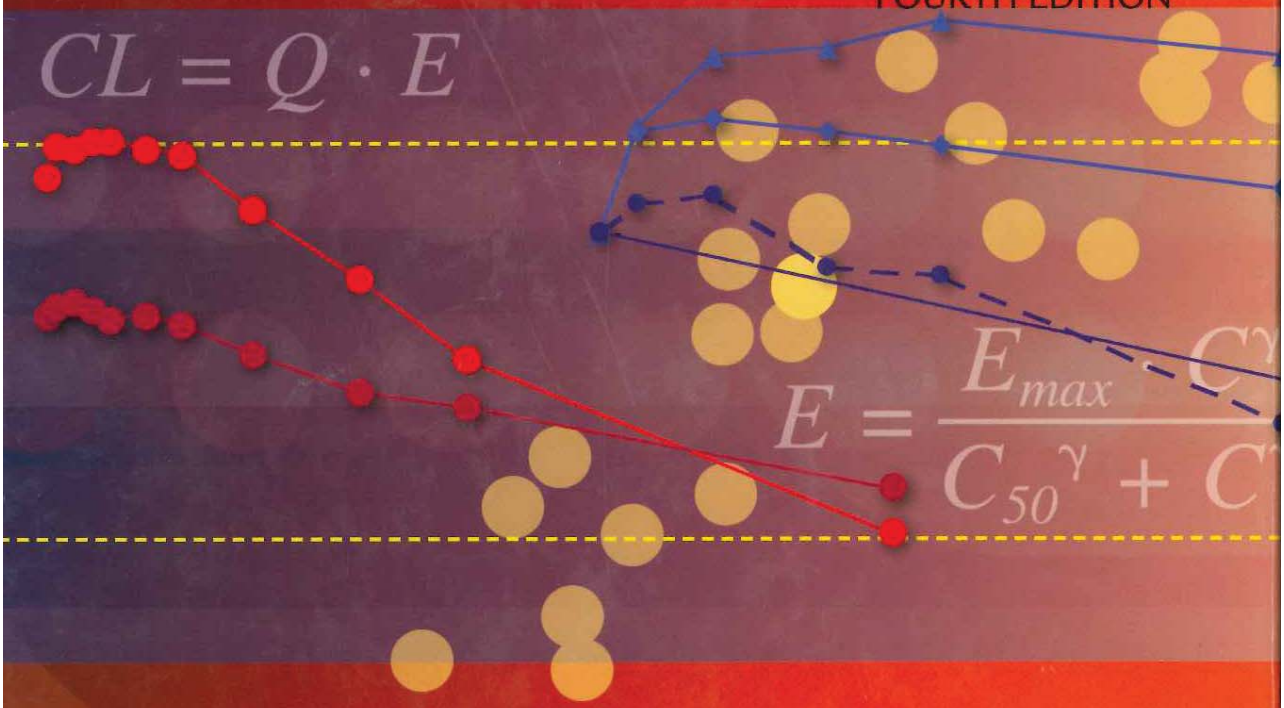


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# Clinical Pharmacokinetics and Pharmacodynamics

## Concepts and Applications

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Another very important factor is the **maximum effect** of the drug. That is, the greatest possible effect, $E_{max}$, that can be achieved with the compound. Returning to the example of ketamine, it is apparent that however high we increase the concentration of R(−)-ketamine, we can never achieve the same maximum response as can be achieved with the S(+)-isomer. Clearly, if the desired therapeutic response demands that the effect be greater than can be achieved with R(−)-ketamine, then no matter how potent this compound, it would be of little therapeutic value when given alone. The last important pharmacodynamic factor for a graded response is the steepness factor, $\gamma$. If it is very high, it may be difficult to manage the use of the drug as only a small shift in concentration around the $C_{50}$ causes the response to change from zero to full effect, and vice versa. In contrast, if the value of $\gamma$ is very small, then large changes in drug concentration are needed to cause the response to change significantly, particularly beyond the $C_{50}$ value. Clearly, a value between these two extremes is desirable.

## DOSE–TIME–RESPONSE RELATIONSHIPS

So far, relationships between dose and measures of drug exposure and between response and exposure have been explored. In clinical practice, decisions have to be made as to the dosage regimen to employ to ensure optimal benefit within the confines of the conditions in which the patient receives a drug. This is a complex decision involving consideration of many factors including not only the pharmacokinetics and pharmacodynamics of the drug, but also the nature of the disease being treated, as well as a host of patient factors, both clinical and social. Some of these aspects are considered in the remainder of the book. However, at this point some broad issues, centered on exposure–response relationships, are worth considering.

Drugs are given to achieve therapeutic objectives; the practical question is how best to do so? One approach is to examine the pharmacokinetics of a drug. Figure 2-18 contains typical plots of plasma drug concentration with time following oral administration of a single dose. One may then ask: What feature of the exposure profile is most important in the context of the desired therapeutic objective? In Fig. 2-18A are displayed the concentration–time profiles for two drugs achieving the same maximum concentration ($C_{max}$) and the same time to reach $C_{max}$ ($t_{max}$) but differing in the kinetics of decline in their concentrations beyond the peak. For some drugs intended to be given chronically, it is only important to maintain the plasma concentration above a defined minimum, below which

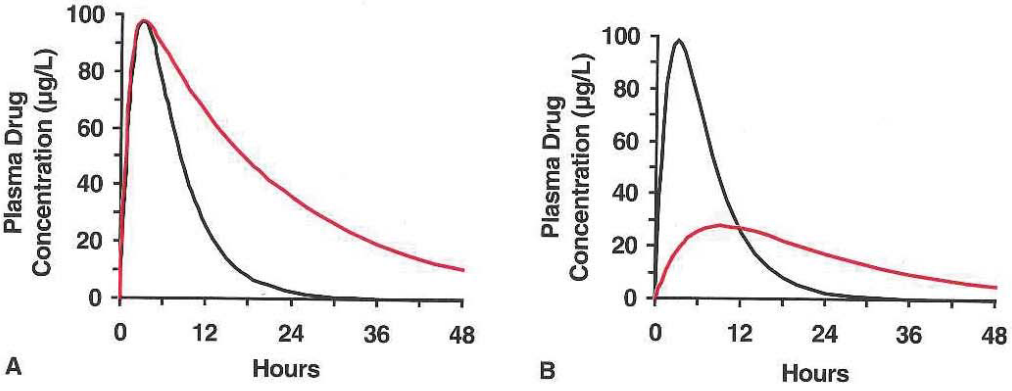


**FIGURE 2-18.** Schematic representations of the plasma concentration–time profiles following a single oral dose. **A.** For two drugs that produce similar peak concentrations and time to peak, but one (colored line) declines more slowly than the other thereby creating a greater total exposure (*AUC*) and higher concentrations at later times. **B.** For a drug that produces the same total *AUC* when given on two occasions, but on one of these occasions (colored line) the peak concentration is lower and later due to a slowing of absorption.