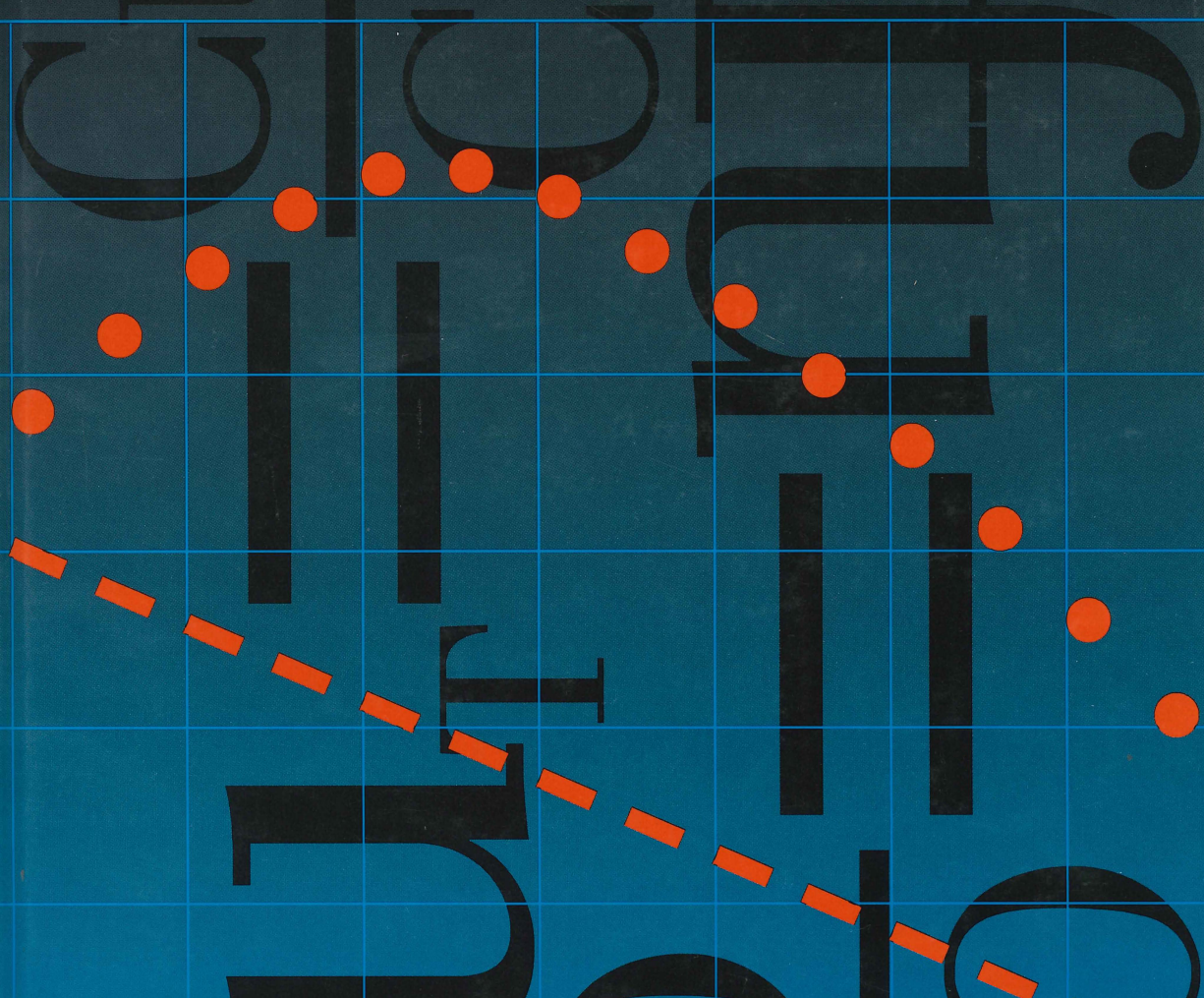# Clinical Pharmacokinetics
Concepts and Applications

third edition

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Therapeutic Window

Let us expand philosophically on this concept of weighting developed for procainamide using the information in Fig. 5–3, adding hypersensitivity and assigning values to the responses according to our best judgment. Figure 5–4 shows the probabilities of the responses, plus that of hypersensitivity, each weighted by a judgmental factor versus the logarithm of the plasma concentration. The factor is negative for undesirable effects and positive for desirable effects. On algebraically adding the weighted probabilities, a *utility curve* is obtained that simply shows the chance of therapeutic success as a function of the plasma concentration. Both low and high concentrations have a negative utility; i.e., at these concentrations, the drug is potentially more harmful than helpful. There is an optimal concentration (8 mg/L) at which therapeutic success is most likely, and there is a range of concentrations (about 4 to 10 mg/L) within which the chances of successful therapy are high. This is the *therapeutic window* or *therapeutic concentration range*. Precise limits, of course, are not definable, particularly considering the subjective nature of the utility curve. Each drug produces its own peculiar responses, and the weighting assigned to these responses differ, but both the incidence of the drug effects and the relative importance of each effect must be evaluated to determine the therapeutic concentration range.

There are problems associated with the acquisition of the incidence of the various responses. For example, the procainamide data were obtained in patients who were sometimes titrated with the drug. That is, the dosage was adjusted when the patient had not adequately responded or when toxicity was present. However, patients even on the usual
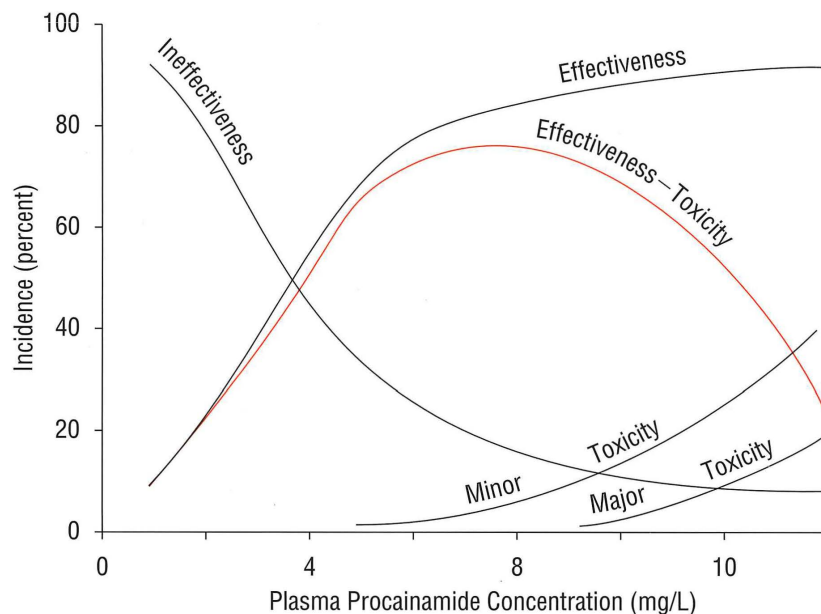

Fig. 5–3. Schematic representation of the frequency of ineffective therapy, effective therapy, minor side effects, serious toxicity, and "therapeutic effectiveness" with plasma concentration of procainamide in patients receiving this drug for the treatment of arrhythmias. Therapeutic effectiveness is defined arbitrarily as the difference in the frequency between effective therapy and toxic effects; the therapeutic effectiveness (colored line) of procainamide reaches a peak of 8 mg/L (1 mg/L = 4.3 μM). (Adapted from the data of Koch-Weser, J.: *In* Pharmacology and the Future: Problems in Therapy. Edited by G.T. Okita and G.H. Archeson. Karger, Basel, 1973, Vol. 3, pp. 69–85.)

Consequently, either the dosing interval necessary to achieve a desired average steady-state concentration or the average concentration resulting from administering the dose every dosing interval can be calculated.

By definition of $C_{ss,av}$, the value of $\tau \cdot C_{ss,av}$ is the AUC within a dosing interval at steady state. Thus, this area is equal to that following a single dose. This principle is shown in Fig. 7–9, and a practical illustration is shown in Fig. 7–10.

Given the plasma concentrations with time after a single oral dose, the concentration at any time during repeated administration of the same dose can be readily calculated by adding the concentrations remaining from each of the previous doses. For example, if doses are given at 0, 12, and 24 hr, then the concentration at 30 hr is equal to the sum of the values at 30, 18, and 6 hr after a single dose.
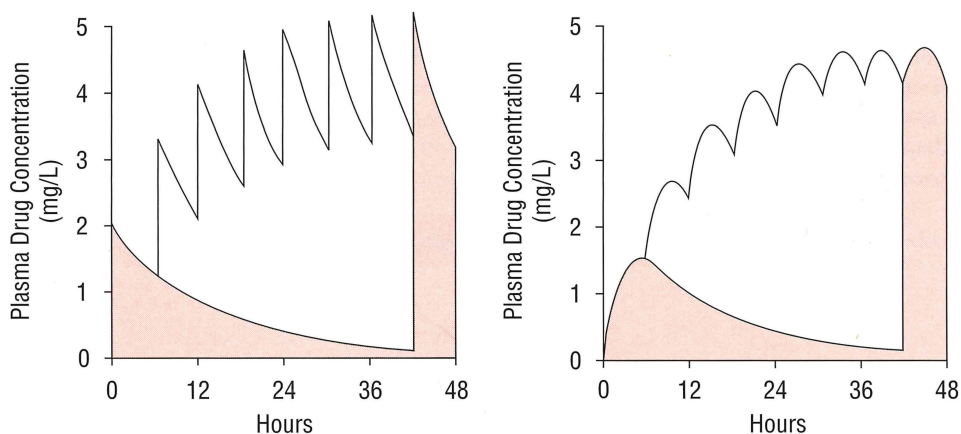

Fig. 7–9. Plasma concentrations of a drug given intravenously (left) and orally (right) on a fixed dose of 50 mg and fixed dosing interval of 6 hr. The half-life is 12 hr. Note that the AUC during a dosing interval at steady state is equal to the total area under the curve following a single dose. The fluctuation of the concentration is diminished when given orally (absorption half-life is 1.4 hr), but the average steady-state concentration is the same as that after i.v. administration, when, as in this example, $F = 1$. The equations used for the simulations are given in Appendix I-D.

Fig. 7–10. Twenty-four subjects each received a single 20-mg oral dose of the benzodiazepine, clobazam, followed 1 month later by an oral regimen of 10 mg of clobazam daily for 22 consecutive days. The observed average plateau clobazam concentration was well predicted by the value calculated from the single dose data, obtained by dividing the AUC by the dosing interval and correcting for dose. The solid line is the perfect prediction (1 mg/L = 33 μM) (Redrawn from Greenblatt, D.J., Divoll, M., Puri, S.K., Ho, I., Zinny, M.A., and Shader, R.I.: Reduced single-dose clearance of clobazam in elderly men predicts increased multiple-dose accumulation. Clin. Pharmacokinet., 8:83–94, 1983. Reproduced with permission of ADIS Press Australasia Pty Limited.)