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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PHARMACOLOGIC RESPONSE

OBJECTIVES

The reader will be able to:

1. Describe, with examples, the relationship generally expected between a graded response and concentration at the site of action.
2. Show graphically how one can readily detect when response is delayed compared to plasma drug concentration after a single dose, and give at least two explanations for the delay.
3. Describe the parameters of the model that often characterize the relationship between response and plasma concentration.
4. Explain why duration of response is often proportional to the logarithm of an intravenously administered dose, and when it is, calculate both the minimum effective dose and the effective half-life.
5. Describe the influence of distribution kinetics on the relationship between duration of response and logarithm of the dose following single i.v. boluses.
6. Show graphically how duration and intensity of response change on repetitive dosing when each dose is given just as the response and concentration fall to predetermined levels for drugs showing one- or two-compartment distribution characteristics.
7. Show why response of reversibly acting drugs declines linearly with time when response is proportional to the logarithm of the concentration and concentration declines exponentially.

The basic principles surrounding the establishment of an appropriate dosage regimen are presented in Chap. 5. These principles rest heavily on there being a functional relationship, albeit sometimes complex, between concentration of drug at site(s) of action and response produced. Some evidence supporting this view is presented in Chap. 5, together with short commentaries on such additional considerations as delays in drug response, role of active metabolites, and tolerance. In this chapter some of these aspects are considered in greater depth and the temporal relationship between dose (or concentration) and response is explored. The chapter begins with an examination of the concentration–response relationship and concludes with a discussion of hysteresis in a plot of response versus concentration.

CONCENTRATION AND RESPONSE

Because sites of action lie mostly outside the vasculature, delays often exist between placement of drug into blood and response produced. Such delays can obscure underlying relationships between concentration and response. One potential solution is to measure concentration at the site of action. Although this may be possible in an isolated organ system, it is rarely a practical solution in humans. Apart from ethical and technical issues that arise,

many responses observed *in vivo* represent an integration of multiple effects at numerous sites. Another approach is to develop a model that incorporates the time-course of drug movement between plasma and site of action, thereby predicting "effector site" concentrations that can then be related to response. Yet another approach is to relate plasma concentration to response under steady-state conditions, which obviates consideration of distribution kinetics. Whatever the approach adopted, the resulting concentration–response relationships for most drugs have features in common. Response increases with concentration at low concentrations and tends to approach a maximum at high values. Recall from Chap. 5 that this was observed for the bronchodilating effect of terbutaline. Such an effect is also seen for the anesthetic ketamine, as illustrated in Fig. 20–1. R(−)-ketamine and S(+)-ketamine are optical isomers which, as the racemate, constitute the commercially available intravenous (i.v.) anesthetic agent, ketamine. Although both compounds have an anesthetic effect, they clearly differ from each other. Not only is the maximum effect (E_{max}) with R(−)-ketamine less than that with S(+)-ketamine, but the plasma concentration required to produce 50% of E_{max}, referred to as the EC_{50} value, is also greater (1.8 mg/L versus 0.7 mg/L). Moreover, the response curve for R(−)-ketamine appears shallower than that for S(+)-ketamine. Although the reason for the differences are unclear, these observations stress the importance that stereochemistry can have in drug response.

General Equation

A general equation to describe the types of observations seen in Figs. 5–1 and 20–1 is

$$\text{Intensity of Effect} = \frac{E_{max} \cdot C^{\gamma}}{EC_{50}^{\gamma} + C^{\gamma}} \qquad 1$$

where E_{max} and EC_{50} are as defined above and γ is the *shape factor* that accommodates the shape of the curve. The intensity of response is usually a change in a measurement from its basal value expressed as either an absolute difference, or a percent change. Examples are an increase in blood pressure and a decrease in percent of neuromuscular blockade.

Although empirical, Eq. 1 has found wide application. Certainly, it has the right properties. Fig. 20–2A shows the influence of γ on the shape of the concentration–response relationship. The larger the value of γ, the greater is the change in response with concen-

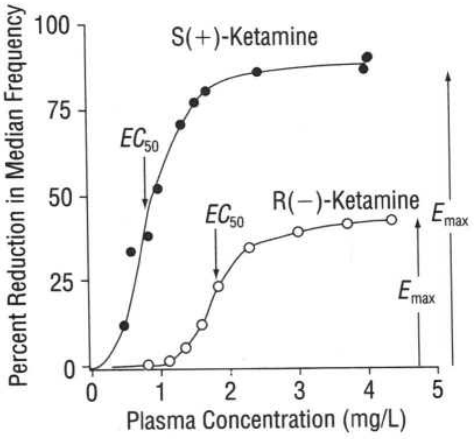

Fig. 20–1. Changes in the electroencephalographic median frequency were followed to quantify the anesthetic effect of R(−)-ketamine and S(+)-ketamine in a subject who received an infusion of these two optical isomers on separate occasions. Shown is the percent reduction in the median frequencies *versus* plasma concentration. Although characteristic S-shaped, or sigmoidal, curves are seen with both compounds, they differ in both maximum effect achieved, E_{max}, and concentration needed to produce 50% of E_{max}, the EC_{50}. These relationships may be considered direct ones as no significant time delay was found between response and concentration (1 mg/L = 4.2 μM). (Redrawn from Schuttler, J., Stoeckel, H., Schweilden, H., and Lauvan, P.M.: Hypnotic drugs. *In* Quantitation, modeling and control in anaesthesia. Edited by H. Stoeckel. Stuttgart, George Thieme Verlag, 1985, pp. 196–210.)

tration around the EC_{50} value. For example, if $\gamma = 1$ then, by appropriate substitution into Eq. 1, the concentrations corresponding to 20% and 80% of maximal response are 0.25 and 4 times EC_{50}, respectively, a 16-fold range. Whereas, if $\gamma = 2$, the corresponding concentrations are 0.5 and 2 times EC_{50}, only a fourfold range. Using the percent decrease in heart rate during a standard exercise as a measure of response to propranolol, the average value of γ is close to 1 (Fig. 20–3). Generally, the value of γ lies between 1 and 3. Occa-

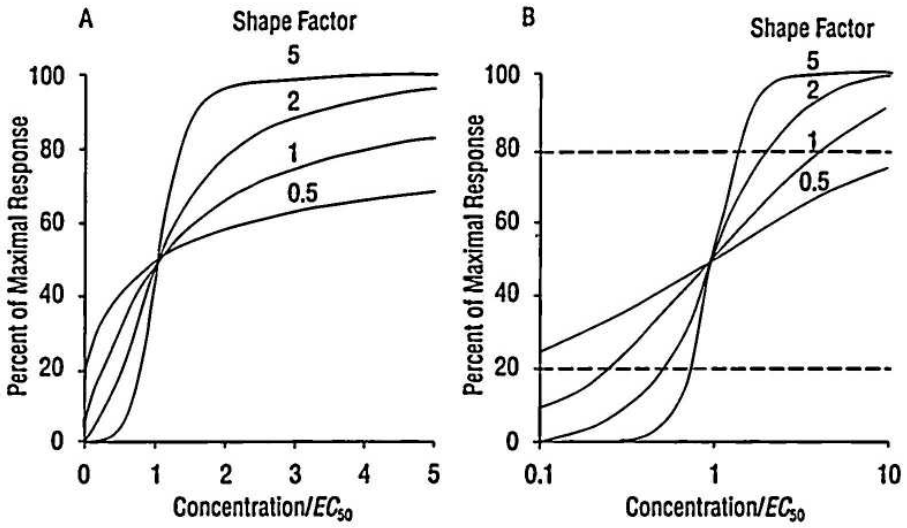

Fig. 20–2. Linear (*A*) and semilogarithmic (*B*) concentration-response plots, predicted according to Eq. 1, for three hypothetical drugs that have the same EC_{50} value but different values of the shape factor, γ. At low concentrations the effect increases almost linearly with concentration (*A*), when $\gamma = 1$, approaching a maximal value at high concentrations. The greater the value of γ, the steeper is the change in response around the EC_{50} value. Between 20 and 80% of maximal effect (colored dashed lines), the response appears to be proportional to the logarithm of the concentration (*B*) for all values of γ. Concentrations are expressed relative to EC_{50}.

Fig. 20–3. Response, measured by the percent decrease in exercise-induced tachycardia, to propranolol increases with the unbound concentration of the drug in plasma. The data points represent measurements after single and multiple (daily) oral doses of two 80-mg tablets of propranolol (●) or a 160-mg sustained-release capsule (○) in an individual subject. The colored line is the fit of Eq. 1 to the data. The response appears to follow the E_{max} model with a γ of 1, an E_{max} of 40%, and an EC_{50} of 5.3 µg/L. (Redrawn from Lalonde, R.L., Straka, R.J., Pieper, J.A., Bottorff, M.B., and Mirvis, D.M.: Propranolol pharmacodynamic modeling using unbound and total concentrations in healthy volunteers. J. Pharmacokinet. Biopharm., *15*:569–582, 1987.)