Pharmaceutical Research, Vol. 4, No. 1, 1987

Commentary

Targeted Drug Delivery—Some Pharmacokinetic Considerations

Gerhard Levy[1]

The great interest in targeted drug delivery makes it important to consider certain pharmacokinetic aspects of this type of drug administration. In its ultimate form, targeted drug delivery is a process whereby the drug is carried or directed by some means to a selected site(s) of action, whereas little or no drug is carried or directly distributed to other sites in the body. In these circumstances, the body will have the pharmacokinetic characteristics of an infinite sink with respect to the targeted drug. Drug elimination from the site of action will them be a function of the kinetics of drug diffusion or transport from the site of action to the rest of the body, of the blood flow rate (microperfusion) through the site of action, of localized biotransformation, or of the rate of dissociation of the drug–receptor complex or other nondiffusible drug complexes that may be formed in the biophase. Conversely, when a drug is administered by conventional (nontargeted) means, the temporal pattern of drug concentrations at the site of action is a function of drug concentrations in the body (particularly in the plasma) and the elimination of the drug is a function of its clearance by metabolic and excretory organs and tissues. These basic differences in the disposition of targeted and conventionally administered drug (Fig. 1) have a number of implications that merit consideration.

Drug targeting should reduce substantially the amount of drug (the effective dose) required to elicit the desired pharmacologic effect. Thus, the effective site-of-action dose (the amount of drug at the site of action, A_E) by targeted delivery will be much less than the effective body dose (A_B) by conventional administration. A_B can be defined as the amount of conventionally administered drug in the body required to obtain an effective site-of-action dose. It is reasonable to assume that, following targeted delivery, a drug will be eliminated from the site of action by diffusion, convection, or transport to the rest of the body, which will act, at least initially, as an infinite sink. Consequently, it can be expected that

(a) drug elimination from the site of action during and following its targeted delivery to that site will, in many cases, be much more rapid than drug elimination from the body as a whole by biotransformation and excretion;
(b) the duration of action of a targeted "bolus" dose, will, in many cases, be much shorter than the duration of action of a conventionally administered bolus dose; and
(c) changes in the biotransformation and excretion kinetics or of other processes (such as the liver perfusion rate) that determine the systemic clearance of a drug by the body will have no effect on the kinetics of elimination of targeted drug from the site of action.

The pharmacokinetic basis of statement b is that the duration of action (t) of a drug is a function of its elimination rate constant k as previously reported (1) such that

$$t = \frac{2.3}{k} \log A_o - \frac{2.3}{k} \log A_{min} \qquad (1)$$

where A_o is the dose and A_{min} is the minimum effective amount of drug. For targeted delivery k represents the kinetics of the apparent first-order process responsible for the removal of drug from the site of action, whereas for conventional drug administration k usually reflects the kinetics of drug elimination from the body as a whole.

Experimental data to illustrate and support these concepts are available from a study by Lyness *et al.* (2), who administered various single doses of different barbiturates to rats by intracerebroventricular injectioin of a 10-μl volume of drug solution and determined the duration of action (hypnotic effect as reflected by loss of the righting reflex). Intracerebroventricular injection of a very small volume of a central nervous system active drug simulates almost ideally the process of targeted drug delivery as defined here. Lyness *et al.* (2) found a linear relationship between the duration of action and the logarithm of the administered dose of barbiturate (Fig. 2), as predicted by Eq. (1). The slope of that relationship for phenobarbital yields a k value equivalent to a half-life of about 20 min, which is very much shorter than the systemic half-life of phenobarbital in rats (~ 1 day). (3). This observation is consistent with concept a.

Chronic administration of phenobarbital is the study by Lyness *et al.* (2) caused enzyme induction (which would be reflected by a decrease in the systemic half-life of the drug) and functional tolerance (which would be evidenced by an increase in the minimum effective dose A_{min}). Notably, the plot of duration of action versus logarithm of dose of phenobarbital for the enzyme-induced animals was shifted to the right [as predicted by Eq. (1) for an increase in A_{min}] but the slope of the plot was essentially unchanged (Fig. 2). This lack of a change in slope indicates that the value of k remained the same, even though the animals were demon-

[1] Department of Pharmaceutics, School of Pharmacy, State University of New York at Buffalo, Amherst, New York 14260.

0724-8741/87/0200-0003$05.00/0

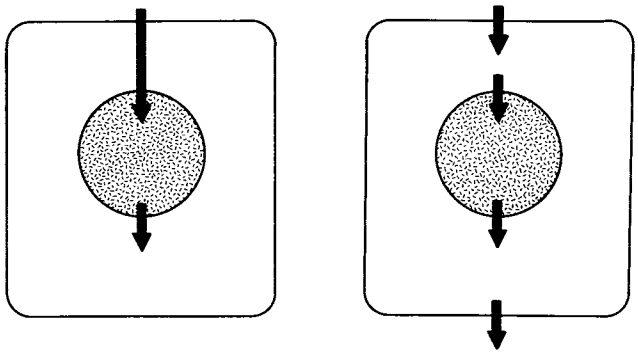

Fig. 1. Basic differences in the disposition of targeted and conventionally administered drug.

strably enzyme induced, and is consistent with concept c and with the underlying assumptions of the discussion (the body acts as an infinite sink; drug elimination from the target site is independent of systemic drug kinetics).

Assuming reversibility of the pharmacologic effect (irreversibly acting drugs are outside the scope of this discussion) and stationarity of the system, a desired intensity of effect produced by targeted delivery of an initial dose of a drug can be maintained by maintaining the effective dose A_E at the site of action. To do that requires continuous targeted delivery at a rate (R_T) which is a function of the k value for drug elimination from the site of action (now designated k_T):

$$R_T = A_E k_T \quad (2)$$

The corresponding relationship for conventionally administered drug is

$$R_B = A_B k_{el} \quad (3)$$

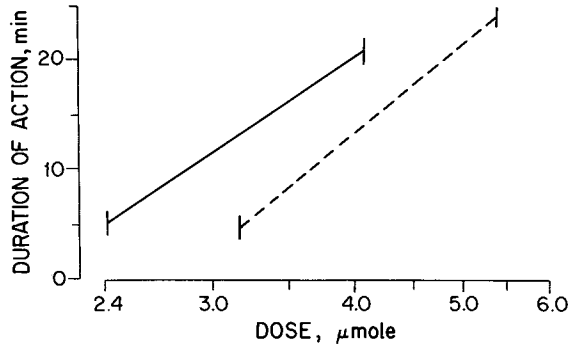

Fig. 2. Relationship between the duration of action and the logarithm of the administered dose of barbiturate.

where R_B is the rate of drug administration and k_{el} is the systemic elimination rate constant for the drug. Since k_T will usually be much larger than k_{el}, the *fractional* rate of drug administration (i.e., R_T/A_E or R_B/A_B) required to maintain a constant pharmacologic effect will be much higher for targeted than for conventionally administered drug. This difference in the relative maintenance dosage has important implications for the design and development of targeted drug delivery systems.

If the difference between k_T and k_{el} is very large, if the ratio of A_E to A_B is not very small, and if k_T does not represent mainly biotransformation at the target site, then drug in the body may gradually accumulate during continuous targeted delivery to a point where the body will no longer have the pharmacokinetic characteristics of an infinite sink. As a consequence, the amount of drug at the site of the desired action, and therefore the intensity of the pharmacological effect, will gradually increase and the selectivity of action inherent in drug targeting will be lost as drug concentrations in the systemic circulation continue to rise. To minimize the likelihood of this loss of selectivity, targeted systems should be designed to require a very low R_T relative to the R_B of the drug. This can be done by increasing the selectivity and specificity of targeting (reducing A_E) or by reducing k_T (analogous to the use of a vasoconstrictor to prolong the action of a local anesthetic in dentistry or the use of a lipid-soluble prodrug that is converted to a water-soluble active compound at the site of action, where it persists due to the restraining effect of a lipoid barrier). It will require very carefully designed pharmacodynamic studies to assess these potential problems in the development and evaluation of targeted drug delivery systems.

ACKNOWLEDGMENT

This work was supported in part by Grant GM 20852 from the National Institute of General Medical Sciences, National Institutes of Health.

REFERENCES

1. G. Levy. *J. Pharm. Sci.* 56:1687–1688 (1967).
2. W. H. Lyness, H. E. Brezenoff, and M. J. Mycek. *Eur. J. Pharmacol.* 54:319–330 (1979).
3. M. Danhoff and G. Levy. *J. Pharmacol. Exp. Ther.* 229:44–50 (1984).