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Maintenance-Dose Prediction Based on a Single Determination of Concentration: General Applicability to Two-Compartment Drugs with Reference to Lithium

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Abstract □ A general approach to the selection of the maintenance dose (D_m) required to give a desired steady-state concentration of drug based on a single determination of concentration after a test dose (C^*) is extended to drugs with two-compartment pharmacokinetic characteristics. Using the equation developed, the value of the proportionality factor relating $1/D_m$ to C^* was found to be within 3.2% of the value calculated from a published nomogram for lithium. The inherent error is shown to be a function of the value of the hybrid rate constants α and β, as well as the value of an intercompartmental transfer rate constant, k_{21}, in an individual.

Keyphrases □ Dose, maintenance—steady-state concentration, prediction by single determination of concentration, two-compartment pharmacokinetics, lithium □ Concentration, steady-state—maintenance dose, prediction by single determination of concentration, two-compartment pharmacokinetics, lithium □ Pharmacokinetics—two-compartment, maintenance dose for steady-state concentration, prediction by single determination of concentration, lithium

In 1973, Cooper *et al.* observed a correlation ($r = 0.972$) between the serum lithium concentration obtained 24 hr after the administration of a 600-mg dose of lithium carbonate and the eventual steady-state concentration if that dose were continued three times a day (1). From that observation, they constructed a nomogram that predicted the maintenance dose required to achieve a therapeutic steady-state concentration of lithium in plasma (0.6–1.2 meq/liter) based on the concentration determined 24 hr after administration of a test dose of the drug. The same group published a report 2 years later confirming the success of the method (2).

Similar techniques have since been proposed for drugs with widely differing pharmacokinetic characteristics (3–9). Montgomery *et al.* (5) proposed that blood samples taken 24 or 48 hr after an oral test dose of nortriptyline could adequately predict steady-state concentrations of that drug using a justification similar to that used by Cooper *et al.* Koup *et al.* suggested that a strong correlation between steady-state levels and drug concentrations 6 hr after administering a single dose of chloramphenicol or theophylline would exist based on a series of pharmacokinetic simulations (7), and later provided clinical data to support the method (8). The appropriate sampling times for those drugs seemed to correspond to their average half-life in the population. It thus became apparent that this approach to maintenance-dose prediction could be applied to many drugs, and that its successful use depended on implicit knowledge of the individual pharmacokinetic characteristics of a drug within the population.

A theoretical framework was provided to explain and evaluate the empirical clinical observations. The theory was founded on the essential clinical observation that there existed an optimal time at which a blood sample could be obtained from an individual, in which the concentration

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of drug would be related to the eventual steady-state concentration by a proportionality factor that could be regarded as being constant throughout the population (10, 11). The theory is consistent with the clinical observations made with chloramphenicol and theophylline. However, the theory suggested that the optimum sampling time for lithium would be ~16 hr after administration of the first dose of drug. The sampling time used clinically (with great success) was 24 hr. Thus, it was possible that the theory did not account for all factors in sampling time optimization. The most obvious shortcoming of the theory was that it was developed for drugs with one-compartment pharmacokinetic characteristics; lithium is a two-compartment drug. It is apparently necessary to extend the theoretical analysis to drugs with biexponential plasma concentration–time profiles, conventionally described by a two-compartment model.

The purpose of this report is to expand the theory to drugs with two-compartment characteristics and to evaluate the source and magnitude of error inherent in the method when it is employed under optimal conditions. We do not report a new dosing method.

THEORETICAL

The development of an expression that relates the maintenance dose (D_m) required to give a desired average steady-state concentration ($\overline{C}_{ss}$) to the concentration in plasma (C^*) at some time (t^*) after the first dose (D^*) for a drug with two-compartment pharmacokinetic characteristics is very similar to the development of the analogous expression for a one-compartment drug (10). Equations pertaining to the intravenous administration of the two-compartment drug will be used even though lithium itself is given orally. If, as in the case of lithium, absorption is rapid relative to distribution and elimination and the bioavailability does not vary between doses, the conclusions based on intravenous dosing will be valid for oral dosing as well. It is also assumed that the values of pharmacokinetic parameters describing the deposition of the drug do not change between the single dose and steady state.

The average concentration of a drug in plasma at steady state $\overline{C}_{ss}$, is defined as:

$$\overline{C}_{ss} = \frac{\int_0^{\infty} C\,dt}{\tau} \qquad \text{(Eq. 1)}$$

where C is the concentration of drug in plasma, t is time, and τ is the time between doses. For a drug with linear, two-compartment kinetics, Eq. 1 can be expressed as:

$$\overline{C}_{ss} = \frac{D_m(\alpha - k_{21})}{\alpha\tau V_c(\alpha - \beta)} + \frac{D_m(k_{21} - \beta)}{\beta\tau V_c(\alpha - \beta)} \qquad \text{(Eq. 2)}$$

where V_c is the volume of the central compartment, α and β are hybrid distribution- and elimination-phase rate constants, respectively, and k_{21} is a first-order rate constant for transfer of drug from the peripheral to the central compartment (12).

The concentration of drug following a single dose is:

$$C^* = \frac{D^*}{V_c}\left[\frac{(\alpha - k_{21})}{(\alpha - \beta)}e^{-\alpha t^*} + \frac{(k_{21} - \beta)}{(\alpha - \beta)}e^{-\beta t^*}\right] \qquad \text{(Eq. 3)}$$

The ratio $\overline{C}_{ss}/C^*$ is therefore:

$$\frac{\overline{C}_{ss}}{C^*} = \frac{D_m}{D^*\tau\alpha\beta}\left[\frac{k_{21}(\alpha - \beta)}{(\alpha - k_{21})e^{-\alpha t^*} + (k_{21} - \beta)e^{-\beta t^*}}\right] \qquad \text{(Eq. 4)}$$

By a rearrangement of Eq. 4, the maintenance dose can be related to C^* by a proportionality factor, ψ:

$$\frac{1}{D_m} = \psi C^* \qquad \text{(Eq. 5)}$$

where

$$\psi = \frac{k_{21}(\alpha - \beta)}{\overline{C}_{ss}\alpha\beta\tau D^*[(\alpha - k_{21})e^{-\alpha t^*} + (k_{21} - \beta)e^{-\beta t^*}]} \qquad \text{(Eq. 6)}$$

Equation 6 shows that the proportionality factor ψ relating maintenance dose to C^* is a complex function of α, β, and k_{21} in an individual. α and β are functions of the intercompartmental transfer and elimination rate microconstants, k_{12}, k_{21}, and k_{10} (12). Equations 5 and 6 will serve as an appropriate means of calculating maintenance dose for a drug with two-compartment behavior when ψ is relatively constant throughout the population, *i.e.*, when each individual's value of ψ is close to the population's mean value of ψ ($\overline{\psi}$). The values of the pharmacokinetic parameters k_{12}, k_{21}, and k_{10} (and therefore α and β) vary among individuals, and one can exert no control over them. The choice of $\overline{C}_{ss}$, τ, and D will depend on the drug used and will have no effect on the variability of ψ between individuals. By the choice of an appropriate value for t^*, the variability of ψ throughout the population can be minimized (10, 11).

Choice of Optimum Sampling Time (t^*)—In selecting the optimum sampling time for a one-compartment drug, the expression for ψ was recast in terms of clearance (CL) and volume of distribution (V). The partial first derivatives of ψ with respect to these independent variables were set at zero, and the resulting expressions were simultaneously solved for time. ψ was found to be minimally affected by interindividual variations in CL and V when t^* was $1/\overline{K}$, where $\overline{K}$ is the mean (or median) value of the elimination rate constant in the population (11). In attempting to do the same for ψ in the multicompartment case (Eq. 6), an explicit value for t^* was not found. Therefore, numerical approximation techniques were used to estimate a value of t^* at which variability of ψ throughout the population was minimal. This approach (described below) has the important benefit of allowing the examination of the behavior of ψ as it approaches its optimum, which provides some insight into the error of the method. By definition, the optimum value of t^* will be that value which produces the minimum variability of ψ throughout the population.

The optimum sampling time (t^*) was selected using parameter values for lithium based on data published by Amdisen (13) and Neilson-Kudsk and Amdisen (14). Fourfold ranges of α and k_{21} centered around mean values of 0.888 and 0.375 hr^{-1}, respectively, were considered. This encompassed the mean $\pm 2SD$ for both parameters. A histogram of β values was constructed from a published histogram of lithium half-life values in 226 patients. The fivefold range of β values was centered about a mean value of 0.065 hr^{-1}; this encompassed the mean $\pm 4SD$ for β. The broader range was used for β because preliminary studies showed that error was most sensitive to changes in β; it was therefore important to cover the entire range of values reported. A program was written to calculate ψ at a given t^* for 125 combinations of α, β, and k_{21}. The numerator of Eq. 6 was plotted against its denominator for various values of t^*. The slope of this plot is $\overline{\psi}$. The coefficient of variation of the estimate of the slope for the best-fit straight line was calculated for each t^* plot. Plots representing the analysis for t^* = 12, 16, 20, and 24 hr are shown in Fig. 1.

The t^* that gives the smallest amount of variation around the regression line, as measured by the smallest coefficient of variation of the slope[1] (or ψ) for the given ranges of α, β, and k_{21}, is the optimum sampling time. In this case, t^* = 16 hr shows the least amount of variation (29.9%) when compared with t^* = 12 hr (37.4%), t^* = 20 hr (33.0%), and t^* = 24 hr (43.8%). A value of 16 ± 1 hr is the optimum sampling time; the other values were chosen for illustrative purposes. This process could be summarized as a plot of the coefficient of variation of the slope *versus* time (which would actually be a plot of the relative variance of ψ as a function of time), where the minimum would represent the optimum sampling time.

Analysis of Error—The use of optimum t^* will give a minimum error in single-point dose prediction methods, but the choice itself does not give an indication of the magnitude or the source of error involved. It has been possible in previous descriptions of one-point maintenance-dose estimation to graphically examine the error of the method by plotting $\psi/\overline{\psi}$ as a function of the variables that determine the value of ψ (11, 16). In this case, $\psi/\overline{\psi}$ would be plotted as a function of α, β, and k_{21} and would therefore be four-dimensional. Such an approach would be helpful, however, if a majority of the variability of ψ among individuals was a function of only one or two of these parameters, allowing a two- or three-dimensional plot to be constructed.

Our investigations of the lithium case have shown that the majority of the variability in ψ through the population was a function of β rather than α or k_{21}. Thus, it would be possible to construct a plot of $\psi/\overline{\psi}$ *versus* β to more closely examine the influence of the major determinant of error. To view the whole problem, however, it is necessary to somehow incor-

[1] Percent coefficient of variation = (standard deviation/mean) × 100. Mean and standard deviation of the slope of the regression line were calculated according to standard methods (15).

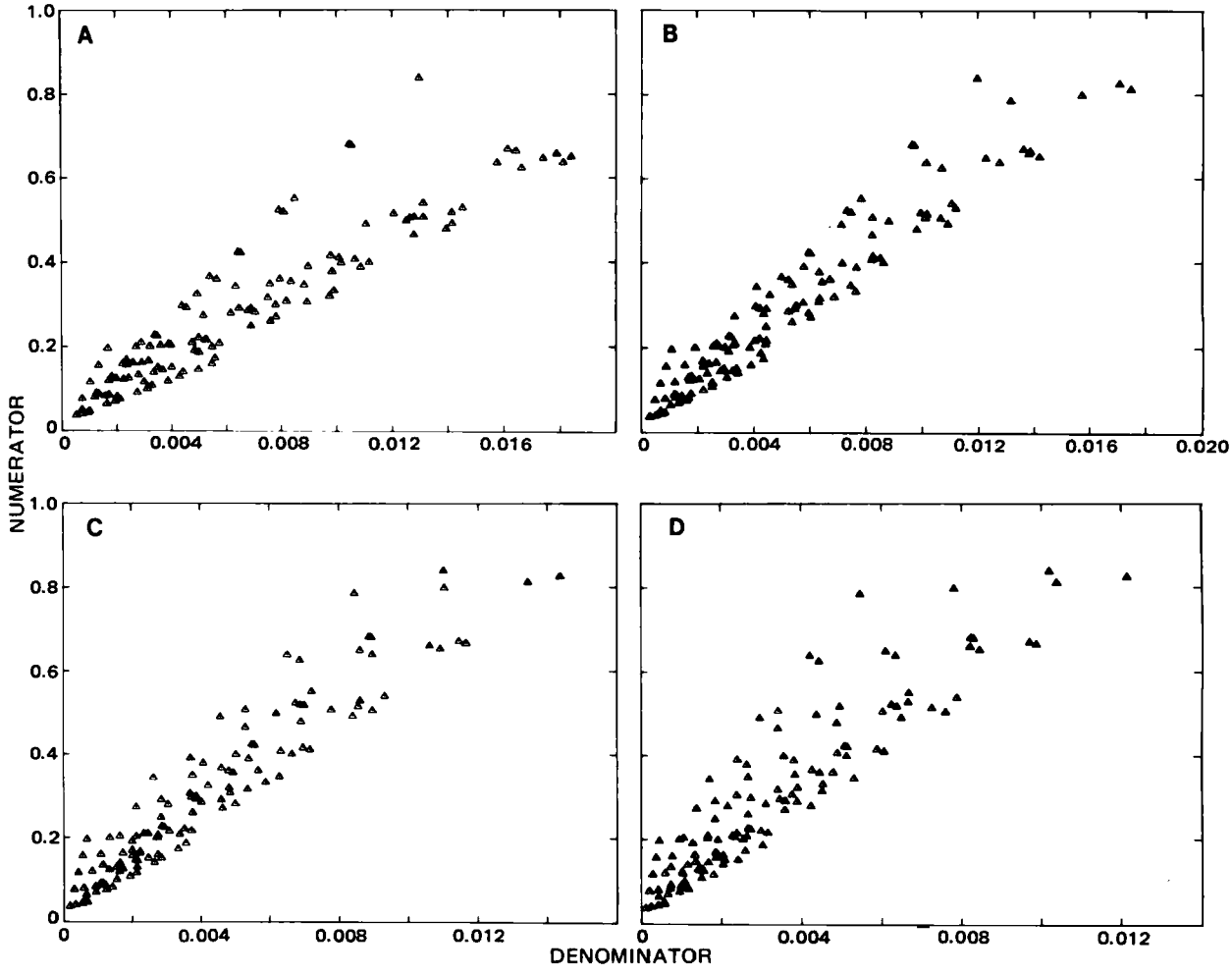

Figure 1—*Optimization of sampling time (t*) for lithium. The numerator of Eq. 6 is plotted* versus *the denominator for values of* α, β, *and* k_{21} *covering the range encountered through the population for lithium (13, 14). The minimum relative scatter is observed for the optimum value of* t*, *16 hr. Key: (A)* t* = *12 hr; (B)* t* = *16 hr; (C)* t* = *20 hr; (D)* t* = *24 hr.*

porate a depiction of the added error due to interindividual variation in α and k_{21}. This was accomplished by random selection of 100 values of α and k_{21} from a normal distribution (based on literature values of mean and standard deviation) for each value of β and calculating the value of $\psi/\overline{\psi}$ for each combination of α, β, and k_{21}. Figure 2 shows the mean values of $\psi/\overline{\psi}$ for each value of β and the magnitude of error due to interindividual variation in β alone, which is analogous to the graphical analysis of error for one-compartment drugs. With t^* = 16 hr, the departure of the plot of $\psi/\overline{\psi}$ from a value of 1 is minimal through the range of values of β covered in the plot. (If ψ did not vary through the population, $\psi/\overline{\psi}$ would always equal 1 and there would be no inherent error in the method.) Values of t^* at 12 and 24 hr give maximum errors of 50–60% at opposite extremes of β, and t^* = 20 hr gives a maximum error of ~40%. When t^* = 16 hr, the maximum error is ~25%.

A more complete analysis of error is obtained from the plots in Fig. 3. The mean value of $\psi/\overline{\psi}$ is again plotted as a function of β, but in this case the mean value is bracketed by ±2 *SD*, as calculated from the aforementioned 100 random combinations of α and k_{21} selected based on published values of their respective mean and standard deviation (13, 14). The maximum error expected to be encountered, taking the variability in ψ due to α and k_{21} into account, is ~40% for t^* = 16 hr and ~100% for t^* = 24 hr. Both of these errors would cause an overdose in patients with unusually large values of β, *i.e.*, individuals with unusually short half-life values.

This method of evaluation of error does not indicate the maximum error which could be encountered in the method, but it does indicate the maximum to be expected in ~95% of the population. Unusual patients could encounter greater error.

Comparison of Theory with a Published Nomogram—The single-point dose prediction for lithium proposed by Cooper *et al.* (1, 2) can be used as a basis for determining the validity of the equations developed here. Their nomogram consisted of seven maintenance doses recommended for seven respective ranges of C^*. Using that nomogram and Eq. 5, a value of ψ was calculated for each value of D_m and the mean C^* for which that dose was recommended. The mean of these values was 6.21 ml/meq·mg. Using Eq. 6; mean values of α, β, and k_{21}; and values of $\overline{C}_{ss}$, t^*, and D^* used by Cooper *et al.* in constructing the nomogram, the value calculated for $\overline{\psi}$ was 6.02 ml/meq·mg. Thus, Eq. 6 and literature data allowed the calculation of a value of ψ within 3.2% of the value found in the clinical experiment.

The agreement between the value of ψ implicitly used by Cooper *et al.* and that calculated using Eq. 6 and literature values of α, β, and k_{21} would seem to indicate that the theory is quantitatively valid. How then can the discrepancy between the optimum sampling time indicated by the theoretical analysis (16 hr) and the sampling time used by Cooper *et al.* (24 hr) in their successful nomogram be reconciled? The choice of optimum sampling time as described above is based on the assumed use of a constant value of ψ throughout the population.

The values of ψ corresponding to the higher ranges of C^* in the nomogram were quite close to one another (coefficient of variation, 11%). However, the value of ψ calculated for the lowest range of C^* for which dosing recommendations were made (mean of this range is 0.025 meq/liter) is 2.12 times the mean value for the higher ranges of concentration.

Patients with low values of concentration will tend to have larger values of β (shorter half-life values) than the population average. The theoretical analysis (Fig. 3) shows that patients with large values of β will tend to be overdosed using the population average value of ψ if the sample to be used for dose prediction purposes is obtained at 24 hr. The published nomogram corrects for this by using a larger value of ψ for these individuals, which reduces the recommended maintenance dose by approximately one-half of what it would be if the value of ψ used in other concentration ranges was retained. The published nomogram, therefore, corrects the error that would be encountered if a constant value of ψ were used

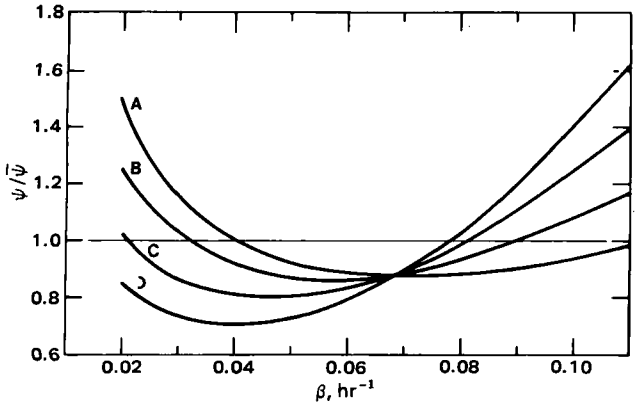

Figure 2—*Relationship between $\psi/\bar{\psi}$ and β for different values of sampling time (t*). α and k_{21} are kept constant at values of 0.888 and 0.375 hr^{-1}, respectively. Key: (A) t* = 12 hr; (B) t* = 16 hr; (C) t* = 20 hr; (D) t* = 24 hr.*

throughout the population by empirically raising the value of ψ in patients who would otherwise tend to be overdosed.

DISCUSSION

The principal purpose of this paper is to examine the single-point maintenance-dose prediction method proposed by Cooper *et al.* for lithium. A more flexible approach has since been described by Sheiner and Beal (17). The single-point method and the Bayesian approach to maintenance-dose selection (17) introduced by Sheiner and Beal have in common a dependence on the knowledge of the distribution of pharmacokinetic parameter values within the population. The Bayesian approach makes use of demographic and pathological information, which is particularly important in the selection of the first dose and in changing the dose as blood level data are obtained. The same sort of information could be incorporated into a single-point method where ψ, t^*, and D^* would be chosen with respect to disease and other factors that affect the relevant pharmacokinetic parameters.

The Bayesian method has additional advantages in that it does not require a sample to be obtained at a particular time and it adjusts the dose as follow-up concentration data are obtained. This method would probably give a more accurate prediction of maintenance dose earlier and with a minimal number of blood samples if the sample was obtained at the time after the first dose which gave the most information about clearance. The optimum t^* considered here and elsewhere (11) corresponds to a blood sample which will serve as the most accurate predictor of maintenance dose required to achieve a desired average concentration at steady state. The proportionality factor between dosing rate and steady-state concentration is clearance. It has been shown empirically and can be shown mathematically that a concentration obtained at t^* will also contain the most information about clearance.

The theory described here is based on the development of a relationship between $1/D_m$ and C^*, which can be described with minimum error by assuming a constant value of a proportionality factor (ψ) throughout the population. If this is done, the error of the method will increase as the extremes of parameter values are approached. A recent report described a case in which a patient with an unusually long half-life and unusually large volume of distribution of lithium was given a dose of lithium carbonate for maintenance of a steady-state concentration of 0.8–1.1 meq/liter which actually led to a steady-state concentration of 2.6 meq/liter and symptoms of toxicity (18). A complete characterization of the pharmacokinetics of lithium in the patient led to the readjustment of his dose to 1050 mg of lithium carbonate (he was given 1800 mg on the basis of the nomogram). Use of this dose led to the attainment of the target steady-state concentration. Substitution of his pharmacokinetic parameter values calculated from the concentration–time plot presented in the report into Eq. 6 led to the calculation of a maintenance dose in close agreement to the 1050-mg dose calculated by classical means. Thus, the failure of the nomogram to predict the correct dose required by this patient was due to his unusual values of β as well as α and k_{21} (all were unusually low). This case illustrates an important limitation of all single-point dose prediction methods: patients with unusual pharmacokinetic parameter values will be improperly dosed. Such methods should therefore be used only as an aid to the selection of a dose that will allow the attainment of a therapeutic concentration of drug with a minimum

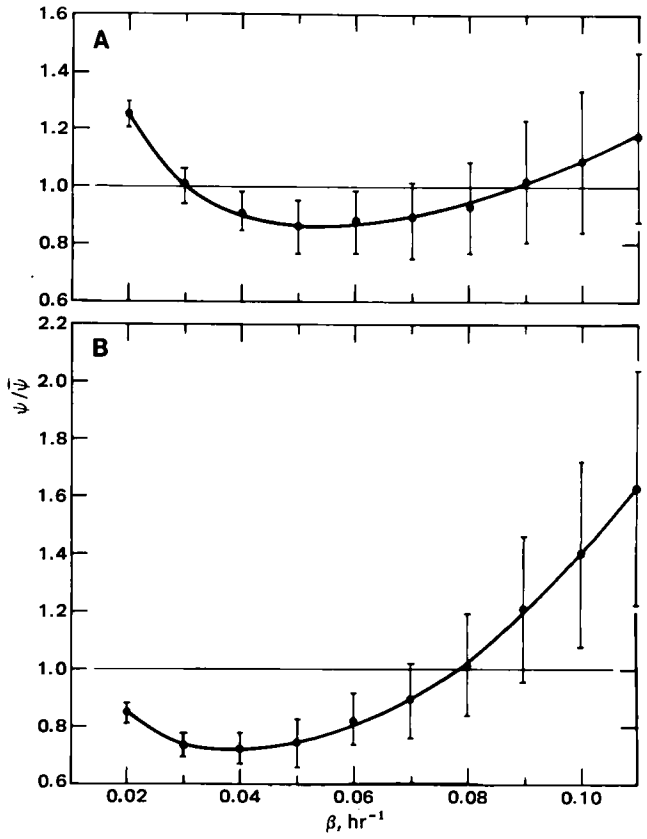

Figure 3—*Relationship between $\psi/\bar{\psi}$ and β for t* = 16 hr (A) and t* = 24 hr (B). Values of α and k_{21} were randomly selected from distributions described in the literature. Bars encompass mean (0) ± 2 SD of the value of the ratio due to variation in the values of α and k_{21}.*

of dosage adjustment. The appropriateness of the dose selected should be confirmed by the determination of concentration after the patient reaches steady state.

The key to the optimization of sampling time described here is the assumption that a single value of ψ will be used for dose prediction purposes for all individuals. The nomogram described by Cooper *et al.* is based on a sampling time 50% longer than the optimum if a constant value of ψ is used. The nomogram is successful because the nonlinearity of the relationship between $1/D_m$ and C^*, when C^* is determined 24 hr after the test dose, is accounted for by using a larger value of ψ in patients with low values of C^*. Such an approach should be possible with other drugs to the extent that low values of C^* correlate with large values of β, rather than large values of volume of distribution. If a low value of C^* is mostly a function of a large volume of distribution, an error due to this parameter will be introduced, which may increase the error beyond that which would be encountered if a constant value of ψ were used.

The theoretically optimum t^* has been shown previously to be the reciprocal of the population mean elimination rate constant based on equations developed for drugs that exhibit a monoexponential decline in plasma concentration. With such drugs, the optimum t^* is, therefore, equal to the harmonic mean of mean residence time (19) in the population. Since mean residence time is a model-independent parameter (its calculation assumes linear kinetics with elimination occurring from the central compartment), it is expected that the harmonic mean of the mean residence time would also be the optimum sampling time for maintenance-dose prediction or estimation of clearance for drugs that exhibit a biexponential decline in plasma concentration.

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Corneal Penetration Behavior of β-Blocking Agents I: Physicochemical Factors

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Abstract □ Rabbit corneas were excised and mounted in a chamber to determine the permeability characteristics of a group of β-blocking agents which varied in octanol–water partitioning over a fourfold logarithmic range. From the permeability rate at steady state, permeability coefficients (pH 7.65) were determined. For each drug the distribution coefficient and pK_a were measured, permitting the partition coefficients to be estimated. Various correlations were determined for the log permeability coefficient as a sum of log functions of the partition (or distribution) coefficient, molecular weight, and/or degree of ionization. The best fit, as judged by a high correlation coefficient ($r = 0.9756$) and lack of systematic deviation, was represented by: $\log P_T = 0.623 \log DC - 0.108(\log DC)^2 - 5.0268$.

Keyphrases □ β-Blocking agents—permeability characteristics, excised rabbit corneas, physicochemical factors □ Permeability—β-blocking agents, excised rabbit corneas, physicochemical factors □ Ophthalmic drugs—β-blocking agents, corneal permeability, rabbits, physicochemical factors

Whenever an ophthalmic drug is applied topically to the eye, only a small amount (<10%) actually penetrates the cornea and reaches the internal eye tissues (1–3). Precorneal factors, such as rapid drainage by the nasolacrimal apparatus and noncorneal absorption, account for the poor absorption (4). As a result, optimal absorption depends on achieving a rapid penetration rate across the cornea to minimize the competing, but nonabsorptive rate factors. Rapid penetration either permits a lower dose to be administered or, in the case of an inactive drug, leads to the development of a clinically effective drug.

The penetration potential of a drug with regard to its chemical structure can be assessed by the use of the partition coefficient of the drug. This has been shown for the cornea by Schoenwald and Ward (5) and by Mosher and Mikkelson (6). Schoenwald and Ward (5) determined the permeability rates across excised rabbit corneas for 11 steroids. Permeability coefficients for each steroid were calculated, and their logarithms were plotted against their respective log octanol–water partition coefficients. A parabolic relationship fit the data, with optimal permeability observed at a log partition coefficient of 2.9. Likewise, Mosher and Mikkelson (6) determined the *in vitro* corneal transport of *n*-alkyl-*p*-aminobenzoate ester homologues. For this series a parabolic equation also fit the data; optimal permeability was observed at a log partition coefficient of 2.5–2.6 (*n*-propyl homologue).

Although relative potency is a significant factor, a rapid penetration rate can contribute significantly to effectiveness. For example, prednisolone acetate (1% ophthalmic suspension) has been ranked as the most effective topical anti-inflammatory agent when the epithelium of the inflamed cornea is intact (7), whereas prednisolone (equally potent orally) is not effective topically. The prodrug di-

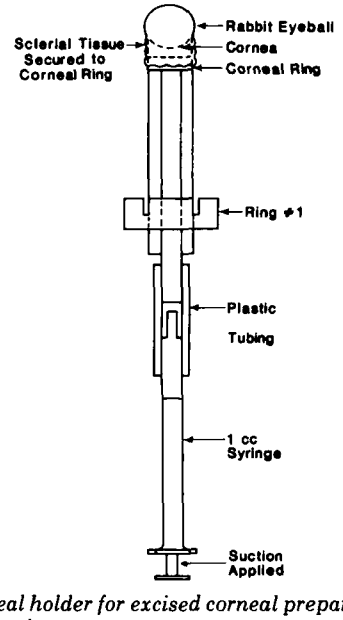

Figure 1—*Corneal holder for excised corneal preparation used in the permeability experiment.*

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