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PREDICTING STEADY STATE SERUM CONCENTRATIONS OF DRUGS

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Mathematical models of biologic processes can be validated both by their ability to provide a framework of understanding for already observed phenomena, as well as by prediction of events that have not yet taken place. Clinical pharmacokinetics is widely accepted as providing useful models for explaining the behavior of many drugs in the human organism. The predictive value of pharmacokinetic models, however, has been tested less extensively and with somewhat less success.

APPROACHES TO PREDICTION

Several methods are used to predict steady state serum concentrations of drugs during multiple-dosing schedules. The particular scheme used for prediction depends on the quantity and source of kinetic data available.

Using an Established Individual Kinetic Profile

Prediction of steady state serum concentrations for a given individual is potentially most reliable when a kinetic profile of the drug in question is already available for that individual. Generation of such data usually involves single-dose drug administration, followed by measurement of serum or plasma drug concentrations at multiple points in time after the dose. Kinetic parameters are then determined by iterative least-squares regression

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techniques or variants thereof. The disposition of most drugs used in clinical medicine can be explained by a linear sum of exponential terms:

$$C = \sum_{i=1}^{j} A_i e^{-k_i t}, \qquad 1.$$

where C is the serum concentration at time t after a single dose. A_i and k_i represent a series of "hybrid" coefficients and exponents, respectively, that can be related to intrinsic rate constants of appropriate compartmental pharmacokinetic models (1, 2).

Based upon usually justified assumptions of linear superimposability of sequential doses, algebraic techniques are used to extrapolate single-dose kinetic behavior to the situation of multiple dosing (1–8). Assuming that a specified fixed dose is administered repeatedly at a specified fixed dosage interval (T), the serum or plasma concentration (C) at any time (t) ranging from 0 to T during the nth dosage interval is given by

$$C = \sum_{i=1}^{j} A_i \frac{1 - e^{-nk_iT}}{1 - e^{-k_iT}} e^{-k_i t}. \qquad 2.$$

Analysis of selected examples of published data utilizing this approach indicate variable accuracy of prediction. Kaplan and associates (9) assessed steady state blood concentrations of diazepam in four volunteers who received 10 mg per day as a single daily dose. Deviation between observed and predicted steady state concentrations in the four subjects were, respectively: –15%, –3%, +16%, and +21%. Although the overall quality of predictability appeared good, there was considerable day-to-day variability in the predose steady state blood concentrations within individual subjects.

Ochs and associates (10) assessed steady state serum quinidine levels during simulated chronic therapy with oral quinidine sulfate and gluconate salts in seven volunteer subjects. Correlations of observed and predicted predose steady state serum concentrations did not reach significance either for the sulfate ($r = 0.45$) or the gluconate ($r = -0.12$) preparations. Dose-to-dose variability in minimum steady state serum levels averaged 7 to 10% with quinidine sulfate and 16% with quinidine gluconate.

Greenblatt and associates evaluated the predictability of accumulation of two benzodiazepines, chlordiazepoxide and lorazepam, in separate studies. Three healthy volunteers participated in the chlordiazepoxide study (11). During once-daily oral administration of 50 mg of chlordiazepoxide hydrochloride, deviation of observed and predicted steady state blood concentrations in the three subjects were, respectively: +44%, –34%, and –22%. As in the diazepam study (9), there was considerable day-to-day variation in predose blood concentrations even within the same individual. In the loraze-

pam study (Greenblatt, D. J., unpublished observations), six volunteers received 3 mg of lorazepam daily on a divided dosage schedule. The dosage schedule was chosen to correspond to those customarily used in clinical practice: either 1 mg t.i.d. (9 AM, 3 PM, and 9 PM), or a b.i.d. schedule with the larger dose administered at bedtime (1 mg at 9 AM, 2 mg at 9 PM). Because the dosage schedule did not involve equally spaced administration of identical doses, accumulation ratios were used to estimate the observed and predicted extent of accumulation. Mean values of observed and predicted accumulation ratios (1.88 vs 1.77, respectively) were not significantly different, but the correlation between the two ($r = 0.51$) did not attain statistical significance. Deviation between observed and predicted accumulation ratios were not explained by changes in the rate of lorazepam administration. For all subjects, values of elimination half-life observed during the single-dose part of the study (mean, 14.2 hr) were nearly identical with the values (mean, 14.9 hr) measured during the "washout" period after multiple-dose therapy was terminated ($r = 0.92$).

Cooper and associates (12, 13) have developed a successful scheme for predicting steady state serum concentrations of lithium. A modified single-dose kinetic study is performed by administration of a single 600 mg "priming" dose of lithium to an individual patient. A single serum lithium concentration determination performed 24 hr after the priming dose is highly predictive ($r = 0.97$) of steady state concentrations achieved during multiple-dose therapy. The relationship allowed the authors to develop guidelines for dosage schedules appropriate for maintenance of therapeutic serum lithium concentrations during multiple-dose therapy in patients with manic-depressive disease.

Mitenko & Ogilvie (14) formulated a scheme for rapid achievement and maintenance of therapeutic steady state serum theophylline concentrations during intravenous therapy. In a study of three volunteers, there was close agreement of observed and predicted steady state concentrations during continuous intravenous theophylline infusion.

This selective review suggests that the availability of a reasonably complete kinetic profile of a particular drug in a specific subject or patient does not always assure accurate prediction of steady state concentrations during multiple-dose therapy. Possible explanations for inaccurate prediction are discussed below.

Application of Population-Based Parameters to Individual Patients

The alluringly direct approach to prediction described above is seldom applicable in clinical practice, because a complete single-dose kinetic profile for a given drug in a patient who initiates multiple-dose therapy with that

drug is not usually available. Thus, prediction of steady state drug concentrations generally requires access to and utilization of information derived from studies of populations (15).

NONADAPTIVE OR MINIMALLY ADAPTIVE MODELS The most straightforward population-based models involve nonadaptive or minimally adaptive application of mean kinetic variables directly to individual patients. Examples are found in schemes for rapid achievement and maintenance of therapeutic plasma concentrations of lidocaine during intravenous therapy (16, 17). The algorithms suggest adjustment of dosage (infusion rate) according to body weight, but otherwise, assumptions about lidocaine clearance are based entirely on mean values reported in the literature. Wagner (18) similarly described an approach to intravenous theophylline therapy based upon mean kinetic parameter variables previously reported in the literature.

This type of approach clearly can enhance conceptual understanding of dosage scheduling requisite for achievement of therapeutic serum concentrations. The method can be of clinical value for drugs whose clearance varies minimally between subjects, thereby maximizing the likelihood that population mean values do in fact apply to a specific individual. Limitations of the method become substantial when population-based kinetic parameter estimates are greatly variable.

MODELS WITH ADAPTIVE INPUT The next hierarchy of sophistication involves an input-adaptation approach (15). Population studies are necessary to provide a data base. Generally, a regression model is used to assess the relative contributions of identifiable characteristics of patient, drug therapy, and disease state that influence steady state serum or plasma drug concentrations. Table 1 lists variables most commonly utilized in such regression models. The prediction format provides either equations or

Table 1 Independent variables used for input-adaptive prediction models

Patient characteristics
Age
Sex
Body weight
Body surface area
Serum albumin concentration
Serum creatinine concentration
Creatinine clearance
Characteristics of therapy
Dose
Dosage interval

nomograms by which identifiable independent variables can be combined to predict steady state serum concentrations at any given dosage. Alternatively, the model can be used to choose the dosage schedule required to achieve a given steady state concentration.

The adaptive approach has had the widest application and most success for those drugs whose total clearance is largely explained by renal clearance (19, 20). In such cases, renal clearance of the drug may be highly correlated with creatinine clearance, thereby allowing direct measurement of a major determinant of total drug clearance, and therefore of steady state serum concentration. Not surprisingly, adaptive models are usually applied to the aminoglycoside antibiotics and the digitalis glycoside digoxin—two drugs having relatively narrow therapeutic indexes, and whose renal clearance accounts for the majority of total clearance. Published studies report varyingly successful prediction (21–28).

The value of adaptive models for predicting steady state concentrations of drugs largely cleared by hepatic biotransformation is much less obvious, because no single, easily measured index of hepatic metabolizing capacity is established. Measurement of clearance of an exogenously administered "marker" substance, such as antipyrine (29) or indocyanine green (30), may serve this purpose, but this requires a kinetic study in itself.

INPUT ADAPTIVE WITH FEEDBACK The most sophisticated population-based predictive models are input-adaptive as described above, but further contain provision for feedback revision of the model following actual measurement of drug plasma concentrations. This approach has been pioneered largely by Sheiner and associates and utilized to predict steady state concentrations of digoxin (31, 32). Although the mathematics are complex, this approach appears to provide an increment of accuracy over other predictive models.

SOURCES OF VARIATION

Potential sources of variation between observed and predicted steady state plasma concentrations are numerous. Some can be identified and quantitated; if the predictive model is appropriately adaptive, prediction accuracy can be enhanced. Other sources of variation that can neither be identified nor quantitated erode the accuracy of predictive models.

Model Parameters Incorrectly Evaluated

Generation of an accurate single-dose kinetic profile (Equation 1) is essential if the mathematical model is expected to extrapolate to the multiple-dosing situation (Equation 2). A common pitfall is that one or more

parameters determined from a single-dose study are inaccurate due to the design of the study. The most common error is overestimation of the smallest ("terminal") exponent (k_i) (i.e. underestimation of the terminal half-life) because the duration of sampling was not long enough to allow reliable estimation of this variable (33). Since the terminal exponent is the major determinant of drug accumulation, the steady state serum concentration during multiple-dose therapy will accordingly be too small, depending on how much the estimated value of the terminal exponent deviates from the actual value. Thus, the duration of single-dose pharmacokinetic studies must be sufficiently long to allow accurate estimation of the smallest of the exponents.

Wrong Model

Observed and predicted behavior during multiple-dose therapy may deviate because the wrong model was chosen to explain the drug's kinetic behavior. Extrapolation of Equation 1 to the multiple-dose situation (using Equation 2) assumes that processes of drug disposition are dose-independent; that is, total clearance remains the same regardless of dose, plasma concentration, and duration of administration.

This assumption is not always correct. A linear sum of exponential terms fails to explain the pharmacokinetics of phenytoin during multiple-dose therapy (34–37). Because phenytoin clearance is "saturable," clearance decreases as serum concentration increases, thereby causing steady state levels during multiple-dose therapy to exceed those predicted by Equation 2. Phenytoin kinetics over a wide range of doses and serum concentrations are better explained by a Michaelis-Menten model of total drug clearance (34–37). Incorporation of saturable or capacity-limited clearance into the predictive model considerably improves the quality of prediction. Similar problems are encountered in studies of propranolol (38–41), although necessary adjustments in the linear model during multiple-dose therapy are not so straightforward.

Total drug clearance also can increase during multiple-dose therapy, leading the linear model to overestimate actual steady-state concentrations. This appears to be the case with such drugs as barbiturates, to which chronic exposure causes increased clearance because of enzyme induction. Corrections necessary in the model also are complicated, inasmuch as changes in clearance appear to depend largely upon the duration of drug exposure (42).

Shift in Kinetic Profile

An accurate single-dose kinetic profile of a drug does not assure reliable prediction of multiple-dose behavior using Equation 2, even if the dose- and

concentration-independent clearance model remains valid. This is because the profile of drug absorption and clearance by a given individual may change from time to time even when the same dose is administered under identical conditions.

Shifts in kinetic profile may be due to changes in patient characteristics or the nature of the underlying disease, or to coadministration of other drugs. A change in body weight or state of hydration, a change in renal function, or an alteration of hepatic function could contribute to an alteration of drug distribution and/or clearance (43, 44). Cardiovascular instability leading to increase or decrease in hepatic blood flow could alter clearance of drugs having high and therefore flow-dependent values of hepatic clearance (45, 46). Congestive heart failure also may alter drug distribution (46, 47). Drug absorption, distribution, and clearance can be influenced by coadministration of other therapeutic agents; the medical literature is replete with examples of this type of drug interaction. Any of the above factors may influence a drug's kinetic profile, and therefore alter its steady state concentration during multiple-dose therapy even if the kinetic model is correct. As described in the previous section, some of these factors can be identified, quantitated, and incorporated into an adaptive model of prediction.

More disruptive to the reliability of predictive models are those shifts in kinetic profile that are seemingly random and unpredictable. Most pharmacokinetic studies focus upon differences between individuals in particular kinetic parameters. Few studies deal with variations within the same subject in drug absorption and clearance. Although data are limited, it appears that the rate and completeness of drug absorption, and of its distribution and clearance, can vary considerably from dose to dose within the same individual (48–51). Understanding of these apparently random and unpredictable variations is incomplete, and they may contribute substantially to deviations of observed from predicted steady state serum concentrations during multiple-dose therapy.

Noncompliance

The failure of many patients to take medications as prescribed is well documented, in both hospital and ambulatory settings. The elusive and inherently nonquantifiable character of compliance-failure can be disastrous to predictive models. Noncompliance can bias the data base that forms the framework of the model, inasmuch as prescribed doses may not accurately reflect those that are accurately taken. Even when reliable individuals comprise the index population, application of the model to predictive situations may suffer because patients simply do not take the medication (52).

COMMENT

The mathematical complexity of approaches to predicting steady state serum concentrations increases with the sophistication of the model. Complex computerized systems can involve considerable cost, but the cost is justified if the predictive system leads to more rational and systematic drug use, with accompanying increases in therapeutic success and reduction in episodes of toxicity. The development and refinement of predictive technology clearly is warranted. However, there is a need for periodic cost-effectiveness evaluation of these methodologies in comparison with more traditional (and less expensive) therapeutic approaches involving clinician implementation of kinetically based therapeutic guidelines together with monitoring and adjustment of therapy using actual serum concentration determinations.

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