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POPULATION PHARMACOKINETICS/DYNAMICS*

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INTRODUCTION

Population pharmacokinetics/pharmacodynamics (PK/PD) can be viewed as a particular approach to a very specific problem, namely quantifying determinants of drug concentration (PK) or response (PD) in a population of patients or as an instance of a new approach to a much broader issue: how to learn what we need to know to administer drugs optimally in clinical settings. We prefer this broader view and will introduce population PK/PD with this orientation. After doing so, we will briefly outline the nomenclature and statistical theory of population PK/PD, present an example of its use, and then review published findings made by using this approach.

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STRINGENT VERSUS NONSTRINGENT EXPERIMENTAL DESIGN

Information regarding the clinical actions of drugs can come from a spectrum of possible data sources. The randomized controlled trial (RCT) stands at one extreme, and the informal impressions of a practicing clinician stand at the other. The dimension defined by these extremes is that of stringency of experimental design. The RCT is a very stringent design, demanding considerable control, for experimental purposes, over what is done to whom and when. A physician's impressions are from a very nonstringent design; almost nothing is done for experimental reasons, and all control is exercised for clinical (therapeutic) purposes. Between these two extremes, so-called observational studies define a spectrum of stringency. Observational studies use observational data, here defined as quantitative patient data gathered in the course of clinical care. Such data may be completely nonstringent with respect to both treatments and observations or nonstringent only with respect to treatments but stringent with respect to periodic data acquisition [perhaps the most famous example of this type is the data base assembled for the Framingham studies (1)]. Indeed, observational data may even impose some restrictions on treatment, for example, requiring that the clinical protocol be followed for dosage adjustment, but (and this is the central point) that the protocol be designed either to maximize individual patient benefit or, at a minimum, not to limit benefit to any notable degree.

It is a curious fact of medical culture that although the RCT is seen as virtually the sole "scientific" way to gather information on the value of the therapeutic agents, most of the studies (or, more usually, individual experiences) that ultimately define the therapeutic potential of a drug are less stringent. This reality undoubtedly reflects in part the formidable costs and logistic difficulties involved in doing large-scale RCTs. It is the thesis of many of us involved in the population approach that observational studies can provide valuable information and should be exploited more extensively.

Indeed, it can be argued that the preference among designs, at any stage in the continuum from drug discovery to knowledgeable clinical use, depends largely on such nonscientific considerations as the urgency of demand, the expense of alternative designs, the need for certainty, the efficacy and toxicity of available alternative therapies, the seriousness of the condition for which a new drug is intended, and others. To make this more precise, consider the following features of alternative data sources: (*a*) ease of data analysis and interpretation, (*b*) certainty of conclusions reached, (*c*) relevance of data to decisions, (*d*) abundance of data, (*e*) expense of data, and (*f*) ethical constraints on gathering data.

The first two criteria favor data sources at the stringent, RCT, end of the

spectrum. Stringent design (notably randomization) ensures that relatively simple methods of data analysis will suffice to contrast the results of treatments and that quantitative probabilistic statements (*P* values) made about these contrasts will be valid. However, to the extent that protocol violations occur and are unreported (when, for example, patients who suspect that they have been assigned to what they perceive as a less beneficial arm clandestinely self-administer alternative therapies), the assumptions underlying the simple analyses will be violated and the validity of conclusions may suffer.

The last four criteria favor data from nonstringent designs. Because stringent designs must, for practical or ethical reasons, be restricted to only a special subgroup of all patients of interest (for example, those most compliant, most available, least ill, and willing to give consent), conclusions drawn from results obtained with such individuals may not be applicable to other types of patients. Observational data typically include a more representative sample of the population of interest. A great deal of such data may be readily available; all that is usually required is the merging of already available computer-readable data gathered for other (usually administrative and financial) purposes. Because of this, the cost per data item is only the marginal cost of data merger and is quite low (the cost of gathering the data to be merged is legitimately charged to the primary purpose for which the data are gathered). In contrast, RCTs are very expensive and all costs must be borne by the study itself. Finally, ethical constraints require that when the therapeutic decisions are made for experimental as opposed to clinical purposes, these may not add excess risk to the treatment. Beyond whatever direct "costs" are incurred in resolving ethical dilemmas, the resolution of these dilemmas may compromise stringent study design; e.g. it may be unethical to use a placebo.

Thus, there are many reasons to prefer alternatives to the RCT, and one's choice among them will depend on circumstances (i.e. the trade-offs discussed above). Therefore, it follows that the technology for interpreting such alternative studies must be developed and tested. Population PK/PD provides such a technology.

REASONS WHY STANDARD MODELS AND ANALYSES WILL NOT WORK FOR OBSERVATIONAL DATA

Observational data are characterized by a number of features that are deliberately avoided in more stringent designs. Notable among these are (*a*) repeated measures, (*b*) imbalance, and (*c*) confounding, i.e. correlation between design and outcome. Each of these presents certain problems in data analysis, and if standard approaches are used, biased and/or imprecise results can be obtained. We will briefly discuss each in turn.

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Repeated Measures

In standard RCT designs, a univariate endpoint, such as "alive at 30 days" vs "dead at 30 days," or "time to recurrence" is usually the focus of interest. Each patient contributes essentially one independent outcome datum, and some typical value (often the mean) of these is to be compared among treatment groups. Clinical reality, in many conditions, consists of treating patients over extended periods, assessing their status (outcome) periodically, and adjusting the treatment as indicated. Considerable information relevant to drug action is often present in these time series of responses, and it is desirable to extract that information if possible. However, to do so requires an analysis model that explicitly recognizes which data are independent (those arising from different individuals) and which are not (those arising from the same individual).

Imbalance

This phenomenon is particularly prevalent in observational repeated measures data: one individual may contribute more data than another. For example, consider estimating the "population" mean diastolic blood pressure response to a drug by using measurements from a sample of just two individuals. If 99 daily measurements are available from the first person and just 1 from the second, would the most efficient estimate of the "population" mean be (*a*) the average of all 100 measurements, (*b*) the average of the average of the 99 measurements from the first person with the single measurement from the second person, or (*c*) something in between? The answer is (*c*), and the exact way to balance the measurements involves such seemingly extraneous considerations as the intraindividual vs interindividual variability of response.

Confounding

One would never deliberately design a study so that treatment is assigned depending on something likely to correlate with response (for example, "treat all the least sick patients with the new drug and all the most sick ones with the old drug") and then ignore that choice in the data analysis. Indeed, the major reason for randomization in clinical trials is to avoid even the accidental occurrence of such biased assignment. Yet biased assignment is standard practice in clinical therapy. For example, one usually titrates doses to achieve a desired response; this leads to a correlation between dose and sensitivity. It is illustrative to consider this particular example in greater detail.

Dose–response trials study the effects of different doses of a drug in patients with the goal (among others, perhaps) of determining the appropriate dosage: If the population distribution of dose–response curves can be estimated, one can determine a reasonable initial dose for a new patient and a method to arrive at an appropriate subsequent dose adjustment, if required.

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In the parallel-dose design, an RCT-like approach, just one of several doses is randomly assigned to each patient and the patient's response is measured at that dose (2). Use of this design only yields good information about population average responses at each tested dose. This is sufficient to demonstrate the average dose–response relationship and to determine the initial dose, but does not provide the information necessary for dosage adjustment [because the shape of the average dose–response curve is not necessarily the same as the shape of any individual's personal dose–response curve; see (3) for a discussion]. More importantly, like RCT designs in general, the parallel-dose design does not resemble clinical practice.

Another RCT-like design, the crossover design, deals with the failure of the parallel-dose design to provide individual-specific information. It assigns several dose levels (administered in random order) to each patient, thus providing information about the distribution of individual dose–response curves. However, its resemblance to clinical practice is, if anything, less close than that of the parallel-dose design.

The ideal study would gather data at several dose levels in at least a majority of patients studied (as in the crossover design), but would do so in a way that resembles clinical practice. In fact, a "dose escalation" design does precisely this. In this design, individuals start at a low dose and move to higher doses at prespecified intervals only for prespecified indications (lack of efficacy and absence of toxicity). Although this design is not strictly observational (a dosage protocol is followed), it is not a stringent design, because treatments (doses) are assigned on the basis of clinical indication (responses). Although the dose escalation design is preferable on clinical grounds, it can provide good information only if properly analyzed. The usual data analysis for the parallel-dose or crossover study is based on a simple linear (analysis of variance [ANOVA], or repeated-measures ANOVA) model. Such a model assigns a different average response to each distinct dose. The standard analysis applied to this simple model essentially estimates the mean value of the distinct responses at each dose as the average of the observed responses at that dose. The significance of the differences in average responses is usually the focus of the analysis, and this is determined by using the F test. There are two important features of this approach when considering the analysis of the dose escalation design. (*a*) The response does not depend on the magnitude of the dose. Response in the ANOVA model is not, of course, independent of dose, as it may differ at each distinct dose, but the analysis does not require that the mean response change in any regular way as the dose does. (*b*) The model is local. Because the ANOVA model has a separate parameter fully quantifying the response at each dose, the response at one dose provides no information about the response at any other.

Consider applying this model and method of analysis to dose escalation

data. Simple ANOVA would lead to badly biased estimates of mean response at higher doses, since the only patients to receive higher doses are those who are relatively insensitive to lower doses. Treating the data as though they came from a crossover design (unbalanced repeated-measures ANOVA—an analysis model that is already far more complex than usually attempted) might or might not help. Under the standard repeated-measures ANOVA model, each individual's response at each dose is assumed to differ from the population average response at that dose by an additive shift. If this adequately reflects reality, the analysis may suffice; if it does not, the analysis may not suffice. What is needed is a model incorporating additional information so the dose escalation data can be interpreted correctly (3). One approach is to assume a parametric form for the individual dose–response curves. The usual one is an hyperbola: response is assumed to asymptote to a maximum (E_{max}) at very high doses, and to achieve half-maximal value at the dose D_{50}. Each individual is assumed to have unique values of E_{max} and D_{50} (and the object of the analysis is to estimate the population mean values of these parameters and their interindividual variability). Analysis of data according to such a model requires a sophisticated "population" approach, the basis of which will be discussed further in the next section. The important point here is that proper interpretation of a repeated-measures design with ignorable confounding [i.e. treatment may depend on observed responses (4)] requires both a global model, and a more sophisticated analysis technique. Current population approaches accommodate both of these requirements.

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POPULATION MODELS AND ANALYSIS METHODS

Models and Parameters

A data model is a mathematical expression that describes an observation in terms of two parts: an explained part and an unexplained part. The explained part is usually a function of certain constants, called *parameters*, and known covariates, called *independent variables*. The unexplained art is usually treated as random (but that does not mean that it is entirely without structure).

In PK/PD, the independent variables are usually such things as dose; time since dose; patient age, weight, and sex; severity and presence of diseases, especially of drug-eliminating or metabolizing organs; history of exposure to drugs and/or toxins; and so forth. PK parameters are such things as bioavailability of a drug preparation, absorption rate, clearance, volume of distribution, and so forth, whereas PD parameters are such things as E_{max}, and D_{50}, as above.

Each individual may have his or her own particular set of parameter values. Usually we are interested in both the population mean and interindividual variability of these values. In the population PK/PD literature, those constants

denoting mean (expected) values of parameters, or proportionality constants that relate renal function, for example, to expected drug clearance (Cl), are denoted θ. Mathematically, one might write

$$\mathrm{Cl}_i = \theta_1 + \eta_i^{\mathrm{Cl}}, \quad 1.$$

where i indexes individuals, θ_1 is the population mean Cl, and η_i^{Cl} is the difference between the population mean Cl and that of the ith individual (Cl_i). If Cl were related to renal function (RF, as measured, for example, by creatinine clearance), one might write instead

$$\mathrm{Cl}_i = \theta_1 + \theta_2 \mathrm{RF}_i + \eta_i^{\mathrm{Cl}}, \quad 2.$$

where θ_1 is now the population mean nonrenal clearance, θ_2 is the mean proportionality constant relating renal clearance to RF, and η_i^{Cl} is the difference between the population-expected Cl for the ith individual ($\theta_1 + \theta_2 \mathrm{RF}_i$), and the actual Cl for that individual.

The interindividual standard deviation of parameters (for example, the standard deviation of the η^{Cl} among individuals) is individually denoted by the symbol ω (e.g. ω_{Cl}), and collectively the set of variances (squared standard deviations) and covariances (related to correlations) among all parameters is denoted by the symbol Ω. Finally, the unexplained part of the data, i.e. the discrepancy between the explained (expected) part and the actual observation, is often called the error. The mean error is taken to be zero (the model is adjusted so that, on average, deviations are neither systematically positive nor systematically negative), and the standard deviation of the error is denoted σ.

A very simple example of a population model can be written mathematically as follows:

$$C_{ij} = \frac{D}{V_i} \exp[-(\mathrm{Cl}_i/V_i)t_{ij}] + \epsilon_{ij}, \quad 3.1$$

$$\mathrm{Cl}_i = \theta_1 + \theta_2 \mathrm{RF}_i + \eta_i^{\mathrm{Cl}}, \quad 3.2$$

$$V_i = \theta_3, \quad 3.3$$

$$\mathrm{var}(\epsilon_{ij}) = \sigma^2; \ \mathrm{var}(\eta_i^{\mathrm{Cl}}) = \omega_{\mathrm{Cl}}{}^2.$$

Here, C_{ij}, the jth observed drug concentration in the ith individual after a single dose of magnitude D, is assumed to arise from a monoexponential PK model and to be observed with an error of ϵ_{ij} (with variance σ^2). Equation 3.2

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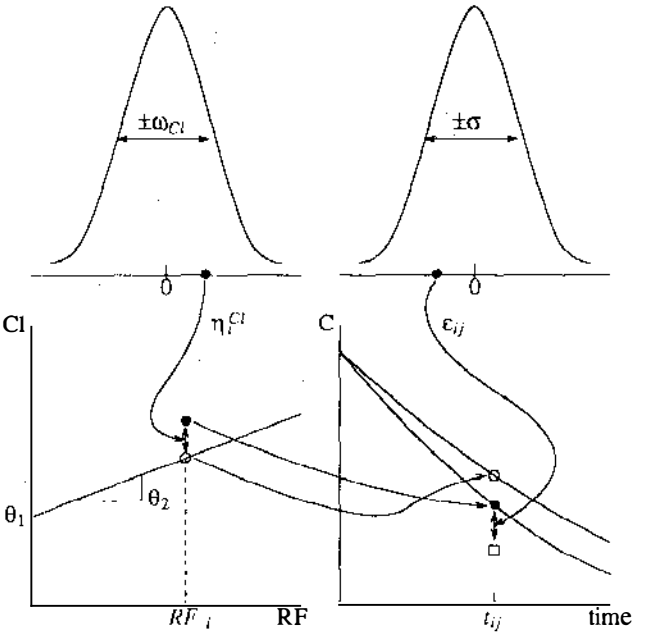

Figure 1 Random and fixed effects influence observations of C_{ij} from the population point of view. The open circle, lower left, is the population parameter predicted clearance, and the solid circle is the true clearance for the ith individual, which differs from population prediction by η_i^{Cl}, chosen randomly from a distribution (upper left) with a mean of zero and a standard deviation of ω_{Cl}. Similarly, lower right, the observed C at time t_{ij} (open square) differs from the true value (solid circle) by an error ϵ_{ij}, chosen independently from a distribution with a mean of zero and a standard deviation of σ. The C corresponding to the population-based prediction is also shown (upper curve, open circle).

for Cl is identical to Equation 2. In a possibly unrealistic oversimplification, interindividual variability is assumed to be present only in Cl, not in V, so that Equation 3.3 states that the V_i are all equal to the same constant, θ_3. Figure 1 portrays this model diagrammatically.

The parameters θ (θ_1 . . .) are useful for adjusting the dosage for known patient conditions (such as renal failure); Ω tells us how much one patient resembles another and thus lets us know how precisely we may estimate therapeutic results a priori. As one treats a single patient, one moves from a view of this patient as typical (mathematically, that his or her parameters are all equal to the population mean values for someone with his or her set of independent variable values) to a view of the patient as unique (as data are used to estimate his or her own particular set of parameters). A formal method of so doing [the so-called empirical bayes method (5)] balances observations

against expectation to discount erroneous observations. This requires knowledge of σ.

Estimation Methods

Estimation methods used for fitting population models to data are generally based on the statistical principle of (normal theory) maximum likelihood (ML) (6). For simple models, this principle justifies the usual least-squares approach, for example. Basically, the probability of the data under the model is written as a function of the model parameters, and parameter estimates are chosen to maximize this probability. This amounts to claiming that the best parameter estimates are those that render the observed data more probable than they would be under any other set of parameters.

If we denote the probability of the data, y, as $P(y; \theta, \Omega, \sigma^2)$, then minimizing the log-likelihood $L(\theta, \Omega, \sigma^2) = -\log P(y; \theta, \Omega, \sigma^2)$ as a function of its parameters $(\theta, \Omega, \sigma^2)$ yields the same estimates as would be obtained by maximizing $P(y; \theta, \Omega, \sigma^2)$ and is numerically more stable. For complex models such as population models, writing $P(y; \theta, \Omega, \sigma^2)$ as some explicit function of θ, Ω, and σ^2 is difficult, and various approximate direct or iterative methods have been proposed to find ML estimates. In our opinion, the most useful direct methods in the PK/PD context are the so-called first-order method (7), which is implemented in the general-purpose population analysis program pacakge, NONMEM (8), and another more recently described method (9). The more interesting iterative methods are based on the so-called EM algorithm (10, 11); such methods have been adapted to PK/PD problems by several workers (e.g. 12–14).

Not all estimation methods for population PK/PD models are normal-theory-based maximum-likelihood methods. In our opinion the most promising other methods are a nonparametric (i.e. nonnormal) maximum-likelihood method (15) and a (normal-theory) bayesian method (16). Maximum-likelihood estimation provides a means of estimating not only the model parameters, but also their standard errors. These can be used for hypothesis tests and confidence intervals. Another method of hypothesis testing is also available. The Neyman–Pearson theorem (17) states that given a model with $p + q$ parameters, if L_{p+q} is the minimum value of the log-likelihood after fitting the full set of $p + q$ parameters, and L_p is the corresponding value after fitting only p of the parameters while holding the other q fixed, then $2(L_p - L_{p+q})$ is asymptotically distributed as chi-square with q degrees of freedom. This is the so-called likelihood ratio test. For example, if one wished to test whether *RF* is relevant to Cl in model 3, the minimum L from fitting data to Equation 3 would be L_{p+q}, while the minimum L from fitting data to model 3 with Equation 1 substituted for Equation 3.2 would be L_p since Equation 1 is Equation 3.2 with θ_2 held fixed to zero. The value of q would be unity, while

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p would be the number of parameters in model 3. The critical value for the 95th percentile of chi square with $q = 1$ degree of freedom is 3.84, so that if twice the difference in the L associated with the fit to the two models exceeded this value, one could reject the null hypothesis that RF is irrelevant to clearance at the $P < 0.05$ level.

AN EXAMPLE

A total of 314 serum theophylline concentrations obtained from 84 hospitalized patients (0.3–15.2 years old) were used in a population analysis of theophylline pharmacokinetics in pediatric patients (18). All concentrations were measured as a part of routine patient care. Information was collected prospectively with the intention that it be used for subsequent analysis. The data base contained both inpatient and outpatient theophylline dosing histories, including the estimated time of the last dose prior to admission, the time of blood withdrawal, age, gender, weight, height, ethnicity, medical history (presence of congestive heart failure, pneumonia, severe pulmonary obstruction, asthma, liver disease, viral infection, recent immunization), and concurrent drug therapy. The purpose of the analysis was to identify how theophylline pharmacokinetics was related to these factors. This would permit the development of computer software to assist the clinician in the individualization of theophylline dosing regimens.

A one-compartment open model with first-order elimination parameterized in volume, V, and clearance, Cl, was assumed. All intravenous doses were modeled as zero-order infusions, and all oral doses were modeled as first-order inputs. A parameter for the extent of oral availability, F, was also included. The NONMEM software package (8) for nonlinear mixed-effect modeling was used and included the specific subroutines required for the pharmacokinetic model.

The model-building phase of the analysis began with the estimation of Cl, V, and F without any covariates. The weighted residuals (WRES) from this step were then plotted against the potential covariates. Factors that appeared to be correlated with the WRES values from this base model were examined for their influence first on Cl and then on V by using subsequent runs. In general, these factors were evaluated one by one through a simple regression relationship (see Equation 2) with the respective pharmacokinetic parameter. The factors examined in this manner included age, total or calculated lean body mass, height, calculated surface area, ethnicity, gender, viral infection, pneumonia and concurrent steroids and/or oral β-agonists. The influence of outpatient dosing and the various oral dosage forms on F were also investigated.

Throughout the model-building phase, a combined proportional and additive error model was used to describe intrasubject variability:

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$$C_{ij} = C_{Mij} + (1 - \theta_x + \theta_x C_{Mij}^2)^{1/2}\epsilon_{ij};\ 0 \leq \theta_x \leq 1, \qquad 4.$$

where C_{ij} is the jth observed concentration for the ith individual, C_{Mij} is the jth model-predicted concentration for the ith individual, θ_x is an iteratively estimated parameter, ϵ_{ij} is the residual intrasubject identically distributed error term with zero mean and variance σ^2. In general, additive intersubject error models were used for each pharmacokinetic parameter during this stage of the analysis.

An alternative to using the WRES plots to identify important covariates has been proposed. First a model without covariates is fit. Then empirical bayes regression analysis (19) is used to estimate individual parameter values based on this model. These estimates are then plotted against the potential covariates (20). This provides a direct evaluation of the relationship between a particular parameter and the covariate. The most recent version of the NONMEM package can directly provide these individual estimates after the usual estimation of population parameter means and variances for the simple pharmacokinetic model.

All the covariates that appeared to have individual, significant influences when added to the model ($P < 0.05$) were combined to form the full regression model. During the model-building phase, age and weight were noted to be highly correlated ($r^2 = 0.890$). Since age alone appeared to yield a slightly better description of the data than did weight alone and since weight in addition to age provided neither an improvement in the fit of the data nor a decrease in the magnitude of the residual intersubject variance in clearance, age alone was included in the full model. The best form for the full model was evaluated by examining different regression relationships between the covariates and the pharmacokinetic parameters. A multiplicative model was slightly better than an additive model, and the parameters were more easily constrained to realistic (nonnegative) values. An additive model can result in a negative pharmacokinetic parameter value during the estimation procedure. In addition, additive and proportional intersubject variance models were examined. The proportional models were preferred for Cl and V. The intersubject variance parameter for F was found to be unnecessary. An additive intrasubject error model, $\theta_x = 0$, was found to be adequate.

The resulting full model was as follows. For clearance,

$$\begin{aligned}\text{LOGCL} = {} & \theta_1 + \theta_2 \cdot \text{AGE}_i + \theta_3 \cdot \text{BLK}_i + \theta_4 \cdot \text{FEMALE}_i \\ & + \theta_5 \cdot \text{AT}_i + \theta_6 \cdot \text{CVI}_i + \theta_7 \cdot \text{PNEU}_i \end{aligned} \qquad 5.1.$$

$$\text{CL} = \exp(\text{LOGCL}), \qquad 5.2.$$

$$\text{CL}_i = \text{CL}(1 + \eta_i^{\text{Cl}}). \qquad 5.3.$$

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For volume,

$$LOGV = \theta_8 + \theta_9 \cdot \text{AGE1}_i, \quad 6.1.$$

$$V = \text{BWT}_i \cdot \exp(LOGV), \quad 6.2.$$

$$V_i = V(1 + \eta_i^V). \quad 6.3$$

For bioavailability,

$$LOGF = \theta_{10} + \theta_{11} \cdot \text{DF1}_i + \theta_{12} \cdot \text{DF2}_i + \theta_{13} \cdot \text{OUT}_i, \quad 7.1.$$

$$F = \exp(LOGF), \quad 7.2.$$

$$F_i = F. \quad 7.3.$$

For intrasubject variability,

$$C_{ij} = C_{Mij} + \epsilon_{ij}. \quad 8.$$

In this set of equations, the individually subscripted variables are as follows: AGE is age in years; BLK is 1 if black race, otherwise 0; FEMALE is 1 if female, otherwise 0; AT is 1 if asthma therapy was oral β-agonists alone, otherwise 0; CVI is 1 if the patient has viral pneumonitis or viral gastroenteritis, otherwise 0; PN is 1 if the patient has pneumonia, otherwise 0; AGE1 is 1 if age is less than 5 years, 0 if 5 years or older; BWT is total body weight in kilograms; DF1 is 1 if the dosage form received was Theodur Sprinkle, Marax, or Somophyllin-T, otherwise 0; DF2 is 1 if the dosage form received was Slo-Bid Gyrocaps, otherwise 0; DF1 and DF2 both are 0 if the dosage form received was Theodur, Somophyllin Elixir, Elixophyllin, Theovent LA, or Tedral; OUT is 1 if recent dosing events included outpatient dosing, otherwise 0; Cl_i and V_i are the (hypothetical) true pharmacokinetic parameters for individual i, Cl and V are the clearance and volume as predicted by the regression model, η_i^{Cl} and η_i^{V} are randomly distributed terms with zero mean and variances ω^2_{Cl} and ω^2_V, respectively, that distinguish the Cl and V of the ith individual from those predicted by the regression model, C_{ij} is the jth observed concentration for the ith individual, and C_{Mij} is the jth observed concentration predicted by the model for the ith individual. This latter value includes the contribution of the η_i^{Cl} and η_i^{V} terms. ϵ_{ij} is the residual intrasubject error with mean zero and variance σ^2.

Each covariate in the full model was then tested for significance ($P \leq 0.005$) in the presence of all other covariates by setting its associated parameter to a fixed value, usually zero, and refitting the model. From such runs the

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influence of viral infection and pneumonia on clearance, the influence of age on volume of distribution, and the estimation of a mean F value different from 1 for Theodur, Somophyllin Elixir, Elixophyllin, Theovent LA, and Tedral theophylline dosage forms appeared to be unimportant. This was confirmed by testing the objective function for the reduced model without these terms against that for the full model. The observed change in the objective function value was 6.1, versus a critical value of 14.9 ($P = 0.005$, 4 degrees of freedom).

Since age and body weight are the only continuous variables, the final regression model (suppressing the subscripts) can be expressed as

$$\text{Cl(liters h}^{-1}) = 0.79 \cdot (1 + 0.35 \cdot \text{BLK}) \cdot (1 - 0.20 \cdot \text{FEMALE}) \cdot (1 - 0.32 \cdot \text{AT}) \cdot \exp(0.092 \cdot \text{AGE [years]}), \quad 9.1.$$

$$\omega_{\text{Cl}}^2 = 0.0341, \quad 9.2.$$

$$V\text{(liters)} = 0.625 \cdot \text{BWT (kg)}, \quad 9.3.$$

$$F = (1 - 0.18\text{DF1}) \cdot (1 - 0.55\text{DF2}) \cdot (1 - 0.21\text{OUT}), \quad 9.4.$$

$$\omega_v^2 = 0.0770, \quad 9.5.$$

$$\sigma^2 = 7.74. \quad 9.6.$$

Thus, clearance is related to black race, gender, concurrent therapy with oral β-agonists, and age. Volume is related to total body weight, and the bioavailability factor is related to certain dosage forms and outpatient dosing. Some previous traditional studies have reported similar findings for gender (21–23). The age-based model yields clearance estimates very similar to those predicted from weight-based models (18). The residual variabilities in Cl and V, expressed as coefficients of variation, are 19 and 28%, respectively. The standard deviation for intrasubject variation is 2.8 μg ml^{-1}. An evaluation of this population model revealed that it was comparable in predictive performance to models developed by using more traditional pharmacokinetic methods (24).

SUMMARY OF RESULTS OBTAINED WITH POPULATION METHODS

Simulation Studies

It is always desirable to evaluate the performance of complex data analysis methods by using Monte Carlo simulations. In this way the results provided

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by the method can be compared with known, true values. A series of three papers (25–27) examined the bias and precision of the first-order method as implemented in the NONMEM system (8) when applied to data generated by a steady-state Michaelis–Menten model, a multiple-dose monoexponential model, and a single dose biexponential model. The first order method was superior to the standard two-stage method, ordinary least squares, and weighted least squares. The standard two-stage method is the traditional method of first determining independent, individual parameter estimates and then calculating sample means and variances from these. This confounds intersubject and estimation error variability. The bias and precision of the parameter estimates obtained by the first-order method were generally acceptable, with variance parameters obviously being more difficult to estimate than typical kinetic parameters. The first-order method has a known potential for providing modestly biased estimates (26), as illustrated by Rodman and Silverstein (28). White et al (29) evaluated parameter estimates for a monoexponential, multiple-dose situation and found that biased estimates are much more likely when residual intersubject and intrasubject variabilities are very high. Modifications to the first-order method that reduce the bias will soon be available in NONMEM (S. L. Beal & L. B. Sheiner, personal communication).

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Population Pharmacokinetic Studies

More than 40 studies of population pharmacokinetics have been performed to date by using methods that appropriately estimate variance components. A variety of drug entities have been involved, and numerous important covariates have been identified. These studies and their most pertinent results are summarized in Table 1. Of particular interest are the studies in neonates, infants, and children. These groups of patients are difficult to study by using traditional methods that rely upon a large number of samples per individual. The population approach, with its ability to extract information from sparse data, is ideally suited for learning about the pharmacokinetics of a drug in groups of patients who have limited blood volume or for whom venipuncture is particularly traumatic.

Drug Interaction Studies

Several studies referenced above have yielded information about drug interactions. In some cases specific analyses were performed with the primary goal of determining the presence or absence of a drug interaction. Alprazolam was found to decrease the apparent clearance of imipramine, and the magnitude of the decrease was related to the alprazolam concentration (72). Amiodarone was shown to increase the elimination rate constant of mexilitine when administered concurrently (73).

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Table 1 Results of population pharmacokinetic analyses

Drug	Data[a]	Results[b]	Reference
Alfentanil	45 patients; 614 *C*'s	V_c was related to body weight. Cl and K_{31} decreased with age over 40 years. Duration of anesthesia had no effect. Residual variability in Cl and V_c were 48 and 33%, respectively.	30
Alfentanil	88 patients including 13 pediatric, 21 geriatric, 11 cirrhotics, 6 cimetidine (inhibitor); 8–12 *C*'s/patient	Disparity between analytical laboratories was detected. Cl was decreased with age, cirrhosis, and cimetidine and was increased in pediatric patients.	31
Alprazolam	10 subjects; 48 *C*'s/subject	The first-order method yielded results identical to traditional methods even when only three predose concentrations per subject were used for the population analysis.	32
Aminoglycocides			
Gentamicin	113 neonates; 2–4 *C*'s/patient	Cl was reduced in neonates with postconception age ≤34 weeks and 5-min Apgar score of <7. Residual intersubject variabilities in clearance and volume were 26 and 16%, respectively. Covariates can be treated as random variables.	33, 34
Gentamicin	143 infants and children; 2–4 *C*'s/patient	*V* was related to body weight, but the proportionality factor was larger in children less than 3 months than in older children. Cl was also related to body weight.	35
Gentamicin	20 patients; 177 *C*'s	*V* and *K* estimates obtained by a nonparametric EM algorithm and the standard two-stage method were the same.	36
Gentamicin	84 preterm infants	Cl was a function of body weight, age, and gestational age. *V* was related to weight. Intersubject variabilities in Cl and *V* were 24 and 27%, respectively. Residual intrasubject variability was high, 41%.	37

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Table 1 (*Continued*)

Drug	Data[a]	Results[b]	Reference
Tobramycin	97 patients; 1–9 *C*'s/patient	Cl was related to creatinine clearance; V_c was related to body weight. Intersubject variabilities in Cl and V were 32 and 3% respectively. Residual intrasubject variability was 21%.	38
Anticancer agents			
Adriamycin	10 subjects	Only macroconstants were estimated.	39
C1941 (an anthrapyrazole)	23 patients; 10–15 *C*'s/patient	Generally good agreement between the standard two-stage and an iterated two-stage method was found.	40
Methotrexate	10 patients; 86 *C*'s	Only macroconstants were estimated.	41
Mitoxantrone	22 patients; 317 *C*'s	Estimation of macroconstants. Calculated intersubject variabilities in Cl and V_d were 46 and 51% respectively.	42
Suramin	36 patients; 325 *C*'s	Parameter estimates were consistent with the results from a small conventional study.	43
Batanopride	88 subjects including 46 cancer patients	V_c was decreased in females. There was increased intersubject variability in Cl among patients versus healthy volunteers, 56 vs 21%.	44
Bisoprolol	84 subjects including 38 with hypertension 13 with renal impairment, and 15 with hepatic impairment; 1158 *C*'s	Cl was related to age, serum creatinine, and aspartate transaminase activity.	45
Cyclosporine	188 bone marrow transplant patients; 5–11 *C*'s/patient	Demonstrated the application of the nonparametric maximum-likelihood method to real data. Results are in agreement with previously published information.	46
Cyclosporin	10 renal transplant patients	Cl/*F* decreased over time following transplantation.	47
Dextromethorphan	419 subjects phenotyped for metabolizer status	Fast, intermediate, and slow metabolizers had substantially different *K* values. Evidence for a high first-pass effect in fast metabolizers was also found.	48

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Digoxin	43 outpatients, 50 inpatients; 380 *C*'s	Outpatient concentrations were 72% of the values expected for inpatients when body size, renal function, and dose were accounted for.	49
Digoxin	141 patients; 586 *C*'s (46 urine collections)	Cl and *V* were related to creatinine clearance and body surface area. Cl also differed between study sites. Outpatient measurements were more variable than inpatient measurements. Differences in assay bias and precision were detected.	50
Felbamate	29 patients; 300 *C*'s	Cl was correlated with carbamazepine dose/concentration ratio. Intersubject variability in Cl was about 15%.	51
Indomethacin	83 neonates; 665 *C*'s	Cl was related to weight and postnatal age. *V* was related to weight. Residual variability in Cl was high, 78%, whereas that in *V* was modest, 29%. These results were consistent with previous results.	52
Lidocaine	42 patients including 22 with clinical evidence of CHF	Cl and V_c normalized for body weight were decreased in patients with CHF.	53
Lisinopril	60 patients with hypertension	Cl was found to be a function of age, weight, serum creatinine, and symptoms of CHF. Results were in good agreement with previous results.	54
Lithium	32 subjects	An optimum dose individualized for renal clearance of lithium was estimated.	55
Maprotiline	99 individuals; 1095 *C*'s	*V* was related to body weight. Random samples of 15 and 30% of the data yielded answers similar to those based on 50% of the data.	56
Metaclopramide	45 cancer patients, 83 treatments; 4–10 *C*'s/treatment	Cl was related to body weight and serum alkaline phosphatase. Intersubject variability in Cl, V_c and V_{ss} were 50, 35, and 35%, respectively.	57
Mexiletine	58 patients including 27 with CHF and 8 with abnormal liver function tests	Normalizing Cl and *V* for body weight decreased the intersubject variability in these parameters.	58

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Table 1 (*Continued*)

Drug	Data[a]	Results[b]	Reference
Midazolam	12 patients recovering from cardiac surgery; 20 *C*'s/patient	All six pharmacokinetic parameters for a three-compartment model and their intersubject variabilities were estimated.	59
Phenobarbital	59 preterm infants	Cl was not related to gestational age, gender, duration of therapy or asphyxia. *V* was modestly decreased, 13%, in the presence of asphyxia.	60
Phenytoin	322 patients; 780 *C*'s	V_{max} was related to weight raised to the 0.6 power. The K_m value for patients younger than 15 years was 43% less than that for older patients. The K_m for Japanese patients appeared to be 23% less than that for European patients. Intersubject variability in V_{max} and K_m were 20 and 50%, respectively.	61
Phenytoin	37 patients; 100 *C*'s	K_m value for black South African patients was about 30% lower than for European patients.	62
Phenytoin	49 patients; 21 *C*'s/patient	*V* was related to body weight. Intersubject variability in *V* was 23%.	63
Procainamide	39 patients; 116 *C*'s (14 urine collections)	Cl and *V* varied in proportion to body weight. CHF reduced acetylation and renal clearances. Intersubject variability in Cl and V were high.	64
Quinidine	60 patients; 260 *C*'s	Cl was reduced in patients with severe CHF, liver failure, or decreased creatinine clearance.	65
Theophylline	100 neonates and infants; 391 *C*'s	Cl was related to weight and postnatal age. It was modestly decreased with concurrent parenteral nutrition. Intersubject variability in Cl was 16%.	66

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Theophylline	84 pediatric patients; 314 *C*'s	Total Cl increased with age. High Cl values were associated with male gender and black race. Concentrations were about 20% lower for outpatient dosing. Differences in bioavailability among formulations was detected. Intersubject variabilities in Cl and *V* were 19 and 28%, respectively.	18
Thiopental	64 patients	Intercompartmental clearance was decreased 27% over the age range of 35–80 years.	67
Valproic acid	194 patients	*K* was higher in children younger than 12 years than in older patients and in patients receiving phenytoin, phenobarbital, or carbamazepine.	68
Vancomycin	106 adults with various degrees of renal failure; 342 *C*'s	Cl was 40% greater than predicted by creatinine clearance in patients over 60 years.	69
Vancomycin	93 adults on hemodialysis, including 7 with cirrhosis; 236 *C*'s	Cl was unrelated to age or cirrhosis.	69
Warfarin	163 patients; 613 *C*'s	Cl was modestly dependent on weight, decreased with age, modestly increased by smoking, and significantly increased by concurrent inducers such as phenytoin or phenobarbital. Intersubject variabilities in Cl and *V* were 28 and 44%, respectively.	70
Zidovudine	36 patients; 8 *C*'s/patient (also urinary excretion data)	Metabolic clearance appeared to increase during therapy. Total and urinary elimination rates increased with weight. Urinary elimination was related to serum creatinine.	71

[a] *C*'s, concentration measurements; CHF, congestive heart failure.

[b] Symbols: V_c, apparent volume of central compartment; V, apparent volume of distribution (one-compartment model); V_{ss}, steady-state volume of distribution; Cl, clearance; K_{31}, mass transfer constant from deep peripheral compartment to central compartment; K, elimination rate constant (one-compartment model); V_{max}, maximum rate of elimination (one-compartment model with Michaelis–Menten elimination); K_m, concentration at which rate of elimination is one-half maximum (one-compartment model with Michaelis–Menten elimination).

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Bioavailability Estimates

The use of the population approach for bioavailability assessment has been explored by using experimental data for pseudoephedrine products (74). Not only can the approach provide estimates of mean bioavailability, but also it provides a measure of the intersubject variability in bioavailability. This is of particular interest with regard to the importance of individual bioavailability versus mean bioavailability as an indicator of the bioequivalence of different formulations. The standard errors of the parameter estimates provided by the NONMEM program to calculate confidence intervals for mean bioavailability (74, 75) should be used with caution because they are known to be optimistic (28, 76).

Pharmacodynamics

The first-order method has been used to simultaneously model the pharmacokinetics and pharmacodynamics of thiopental (68), *d*-tubocurarine (77), hydralazine (78), heparin (79), theophylline (80, 81), and atenolol and betaxolol (82). When the electroencephalogram spectral edge was used as a measure of brain responsiveness to thiopental, no age-related effects were apparent (68). The predose sitting diastolic blood pressure was found to be related to hydralazine dose, body weight, duration of therapy, concurrent β-blocker therapy and acetylator phenotype (78). Gender and age were found to influence both the pharmacokinetics and pharmacodynamics of heparin (79), in agreement with previous studies. The relationship of forced vital capacity to theophylline concentrations has been found not to depend on covariates (80). A recent study has related peak expiratory flow rate to theophylline concentrations (81) and duration of therapy. Maximum improvement was 20% smaller in females than in males and decreased 1.7% per year in patients over 40 years of age.

Bayesian Dose Adjustment

The results of a population analysis provide the information required to individualize initial dosing regimens based on expected (mean) pharmacokinetic and pharmacodynamic parameter values for specific patient characteristics and yield estimates of intersubject and intrasubject variability required for bayesian feedback adjustment of dosage regimens (19, 83, 84). This approach to dosage adjustment balances the uncertainty in the individual's parameters against the uncertainty in the measurements of concentration or response. Examples of the successful use of this methodology can be cited for many drugs, including digoxin (85), phenytoin (86), lidocaine (87), theophylline (88), methotrexate (89), alfentanil (90), and cyclosporine (91). Several reviews describing the clinical utility of feedback control have been published (92–95).

FINAL COMMENTS

Although the population approach to modeling and analysis may be of some value when applied to data from stringent, RCT-like designs, its major value and the motivation for its development have been its promise to provide analyses of observational data or less stringent experimental data. Attempting to use such data to learn about drugs and their actions is relatively new as a formal pursuit and is controversial. Nonetheless, it is our belief that as we acknowledge that political, economic, and humanitarian considerations have a legitimate place in determining what data we may gather and how long we may take to do so; that we do an injustice to patients and the public by failing to exploit all data fully, or by gathering only limited data, or by focusing on only limited analyses; and that we learn by increments, always melding new data with past knowledge, it will become increasingly desirable and necessary to use observational data sources, and, consequently, methods of population modeling and analysis.

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