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POPULATION PHARMACOKINETICS: FUNDAMENTALS, METHODS AND APPLICATIONS

Sara E. Rosenbaum*, PhD, Alison A. Carter, PhD, and
Michael N. Dudley, PharmD

*Department of Applied Pharmaceutical Science
College of Pharmacy, University of Rhode Island
Kingston, RI 02881
and
Antiinfective Pharmacology Research Unit
University of Rhode Island College of Pharmacy
Roger Williams Medical Center
Providence, RI 02908

ABSTRACT

The application of pharmacokinetic principles can maximize the goals of drug administration from the time a drug is first administered to man during the initial phases of development, to well beyond the approval of the NDA. Population pharmacokinetics is playing an increasing role in this regard. This paper provides a comprehensive review of the principles and methods of population pharmacokinetics. Finally, examples of how population pharmacokinetics may be applied to optimize drug administration are presented.

INTRODUCTION

Role of Pharmacokinetics In Drug Action

Before an investigational drug is administered to the first human subjects, *in-vitro* studies and/or animal studies will have demonstrated that the drug possesses some beneficial action on a physiological or biochemical process in the body. The action of the drug *in-vivo*, or more specifically, the relationship between the intensity and duration of effect observed and the dose administered, will be a function of the drug's pharmacokinetics and pharmacodynamics (Figure 1).

If the drug is to be given orally, it must dissolve, survive any adverse intra-luminal events, be absorbed through the intestinal lumen and then escape degradation by the liver. The bioavailability of the drug describes its accessibility to the systemic circulation. Once in the systemic circulation the drug will distribute throughout the body, including hopefully the drug's site of action. The relative distribution of the drug to its site of action will be controlled by the accessibility of the site and by the competing events of distribution to other tissues, and elimination from the body. The impact of these latter two processes is quantified by the drug's volume of distribution and clearance respectively.

Pharmacokinetic models provide structure to the relationship between the independent variables of dose and time and the dependent variable(s) of plasma and/or urinary concentration. For example the model below constitutes the simple one compartment model with IV bolus input and uses the pharmacokinetic parameters of clearance and volume of distribution.

$$Cp = Dose/Vd\ e^{-Cl/Vd\ t}$$

The pharmacodynamic phase completes the body's response to the dose (Figure

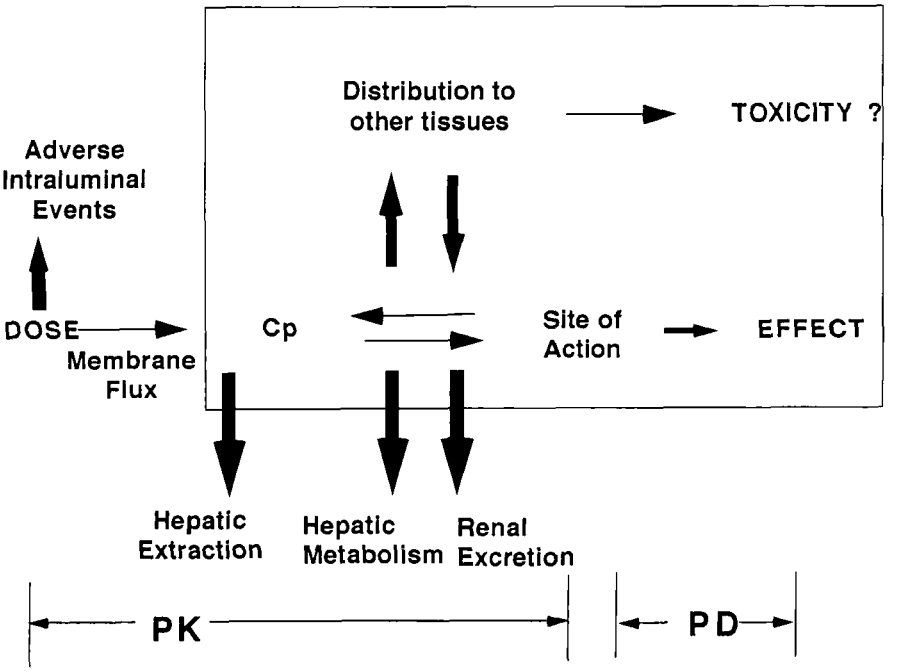

Figure 1. Diagrammatic representation of the relationship between pharmacokinetics (PK), pharmacodynamics (PD) and overall drug response.

1). Once at its site of action the drug may interact with its receptors to produce an effect, which may in itself constitute the response; or perhaps more commonly, the response may occur secondary to the effect. For example, the effect could be inhibition of angiotensin converting enzyme, which leads to a reduction in the synthesis of angiotensin II, which then produces the response, a reduction in blood pressure (1). The relationship between the drug concentration at the receptor site and the response is often described using the sigmoidal Emax model(2,3):

$$E = \frac{E_{max} * C^n}{EC_{50}^n + C^n}$$

Where E is the response, C is the concentration, Emax (maximum response) describes efficacy and EC50 (concentration at 50% response) describes sensitivity or potency. The parameter n governs the steepness or sigmoidicity of the response curve.

In recent years much research has been directed at providing integrated models for drug action (dose-effect) (3). In these models the pharmacokinetic (dose-systemic drug concentration) and the pharmacodynamic models (effect site concentration - effect) are linked. A delay between the effect versus time profile relative to systemic concentrations is frequently observed. The relationship between systemic concentrations and effect is complicated by this delay or lag time, and results in the phenomenon of counterclockwise hysteresis when response is plotted as a function of systemic concentrations, e.g plasma concentration (Figure 2). An effect compartment is frequently incorporated into the model to account for this delay (3). A comprehensive text on this subject is available (4).

POPULATION PHARMACOKINETICS

Population pharmacokinetics is the study of a drug's absorption and disposition characteristics in the population, or a distinct sub-set of the population. Mathematical models are used to summarize this information. These population models explicitly address variability, which can arise from interindividual variability, intraindividual variability, measurement error, e.t.c. Frequently specific patient characteristics, such as renal function, weight, age, gender,e.t.c. account for some of the interindividual variability. Identification of these factors and the modeling of their relationship to specific pharmacokinetic parameters is an important component of the population approach (5). In this way

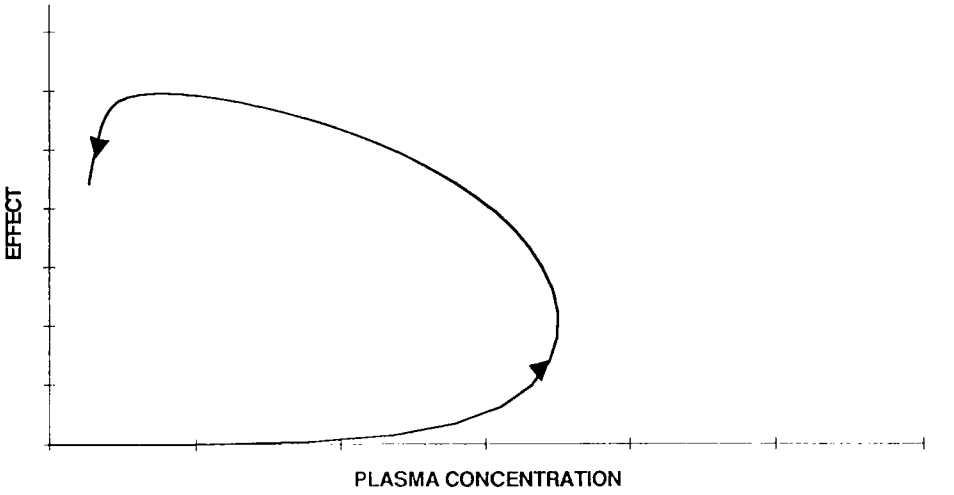

Figure 2. Plot of effect versus plasma concentration for a hypothetical drug. The data were simulated (STELLA II Software, High Performance Systems Inc. Hanover NH) for first order absorption in a one compartment model with a sigmoidal Emax pharmacodynamic model in the effect compartment. The phenomenon of counter clockwise hysteresis is observed due to an equilibration delay between the plasma and effect compartments.

interindividual variability may be partitioned into explainable, e.g. variability in clearance with different degrees of renal function, and unexplainable or random interindividual variability.

METHODS IN POPULATION PHARMACOKINETICS

A circular pattern exists between the population and the individuals within the population. Population models are derived from the individuals; a primary application of population models is the determination of the pharmacokinetic parameters of individuals. Moreover, as a result of the developments in population pharmacokinetics over the last 15 years, the question can now be posed, analogous to the question regarding the relative order of the chicken and

the egg, what comes first the individual or the population?. The answer to this question provides an important way of distinguishing the newer methods of analysis from the traditional ones. Traditional methods start first with the individual and then progress to the population, whereas the newer approaches go directly to the population without first evaluating individuals.

Another important difference in the various methods is the extent to which the random variability is partitioned. In traditional approaches random error from all sources (unexplainable interindividual variability, intraindividual variability and measurement error) is combined, whereas, some of the newer methods separate the unexplainable interindividual variability from the residual random error (intraindividual variability, measurement error, model mis-specification e.t.c). A more extensive discussion of methods in population pharmacokinetics has recently been published (6).

Traditional Standard Two Stage Method

The standard two stage method (STS) is the traditional method used to derive population models. It often involves the study of a relatively small number of individuals who are subjected to intensive sampling. The period of study is often short since the subjects are usually institutionalized. Each individual's data are then analyzed on a case by case basis using weighted or extended non-linear least squares regression to determine individual pharmacokinetic parameters. In the second stage, the individual parameters are then pooled to provide measures of central tendency (means) and variability (variances) for the population. Finally, the association between specific pharmacokinetic parameters and demographic characteristics is studied, e.g. clearance and renal function, or volume of distribution and weight.

The STS method is the classical approach for estimating the average pharmacokinetic parameters of a population and, when an extensive number of samples are available for each individual, provides reliable, robust estimates (7). It is a simplistic method in comparison to some of the more sophisticated direct population methods because, unlike the more sophisticated methods, it does not separate the residual interindividual variability from the other random effects (intraindividual error, measurement error, e.t.c). However, the STS method is capable of producing estimates of typical values for members of a population that are similar to those found with the direct population approaches (8,9,10). In the case of sparse data, however, the direct population methods exceed the capacity of the STS (11). Even as many as 5 samples per patient may yield poor individual pharmacokinetic estimates which, when combined with the other individual parameters, have the potential to produce biased and/or suboptimal population estimates (8).

The advantage of this approach is that it is well tried and rather straightforward to implement, there are many software packages available and the statistics are straightforward and familiar to investigators. In the case of rich data, the STS method is considered to be the gold-standard by which to compare the newer direct population approaches discussed below. However, it has several shortcomings. Since it requires a controlled study, it is expensive and requires careful planning and implementation. Consequently, it may be difficult to study a sufficiently large number of individuals to adequately represent the population. Moreover, ethical issues associated with obtaining extensive samples in the more fragile sub-populations (the very old, the very young, the very sick, people in varying stages of renal disease) make it difficult to obtain information from these groups. Ironically, it is these groups for whom it is so important to apply population pharmacokinetics to optimize drug therapy (see section on Application of Population Pharmacokinetics).

The naive pooling method is another traditional approach to population analysis. Here data from all individuals are pooled and analyzed simultaneously without consideration of the individual from whom specific data were derived. While this method may be the only viable approach in certain situations, e.g. the case of animal data where each animal provides only one data point, generally this approach is considered the least favorable and is most susceptible to bias. Simulation studies have demonstrated that mixing interindividual and random variability in this way produces inaccurate estimates of pharmacokinetic parameters (7).

Mixed Effects Modeling

Mixed Effect Modeling is viewed by many as the optimum population modeling method. It is an example of a direct population approach in which the population parameters are determined in a single stage of analysis applied simultaneously to the data from many individuals (12). However, and in contrast to the naive pooling method, this method recognizes which data arise from the same individuals and which do not.

The "effects" are factors that contribute to the variability of the measured observation and are of two types: fixed and random. Fixed effects are the components of the structural pharmacokinetic model (5,7,13). The structural model itself takes on the usual form. For example,

$$CP = D/Vd\ e^{-Cl/Vd\ t}$$

Where Cp is the observation or dependent variable. The dose (D) and time (t) are the fixed effects and CL and Vd are the fixed effect parameters since they quantify the influence of a fixed effect on the dependent variable.

The fixed effect parameters are often given the symbol *theta*. They may, as in the example above, be the usual type of pharmacokinetic parameters (clearance, volume of distribution). Alternatively, if a pharmacokinetic parameter can be further broken down and explained in terms of patient characteristics, the fixed effects parameters will be coefficients relating the pharmacokinetic parameter to a patient characteristic.

For example,

$$\text{Typical Value of Cl} = Cl_{pop} = \theta_1 + (\theta_2\ Cl_{CR})$$
$$\text{Typical value of Vd} = Vd_{pop} = \theta_3$$

where Cl_{CR} is creatinine clearance

The fixed effect parameters are θ_1, θ_2 and θ_3. In this example Cl has been defined in terms of a linear function of creatinine clearance (Cl_{cr}). The intercept of the relationship is θ_1, which represents the population typical value of non-renal clearance. The slope of the relationship is θ_2 and this represents the mean slope for the population. For the sake of example the other pharmacokinetic parameter Vd is not further broken down and thus itself becomes the fixed effect parameter θ_3 .

Fixed effects do not include any unexplainable variation either between or within individuals. These constitute the random effects and they are divided into two types, random (unexplainable) interindividual variability and residual random error (intraindividual error, measurement error, model mis-specification, e.t.c).

Random interindividual variability is associated with one, more or all of the structural pharmacokinetic parameters, such as clearance, volume of distribution,

e.t.c. Each individual (i) in the population will have a specific value for their pharmacokinetic parameter (e.g Cl_i) which will differ from the population typical value (CL_{pop}) due to unexplainable variability. This variability is quantified using the parameter eta (η) with a subscript corresponding to the pharmacokinetic parameter with which it is associated (e.g. η_{Cl} or η_{Vd}). For the population, eta is assumed to be normally distributed with a variance of ω^2 and a mean value of zero (Figure 3). The manner in which an individual's eta ($\eta_{Cl,i}$) relates the individual's pharmacokinetic parameter (e.g. Cl_i) to the population typical value (e.g Cl_{pop}) is given by the error model. A variety of error models may be chosen, depending on visual inspection of the data (14), experience, and trial and error. Examples include:

$$Cl_i = Cl_{pop} + \eta_{Cl,i}$$

$$Cl_i = Cl_{pop} + Cl_{pop} * \eta_{Cl,i} = Cl_{pop} (1 + \eta_{Cl,i})$$

$$Cl_i = Cl_{pop}\, e^{\eta Cl,i}$$

The other component of the random error is the residual error (intraindividual variability, measurement error, model mis-specification, e.t.c.) and it is equal to the deviation of the observation (usually plasma concentration) from the model-predicted observation. The parameter for random error is given the symbol epsilon (ϵ). Like random interindividual error, it is assumed to be normally distributed and has a variance of (σ^2) (Figure 3).

A second error model is required to incorporate this random residual error. In common with the model for random interindividual error it may take several forms. As an example consider a simple additive model, which relates the plasma

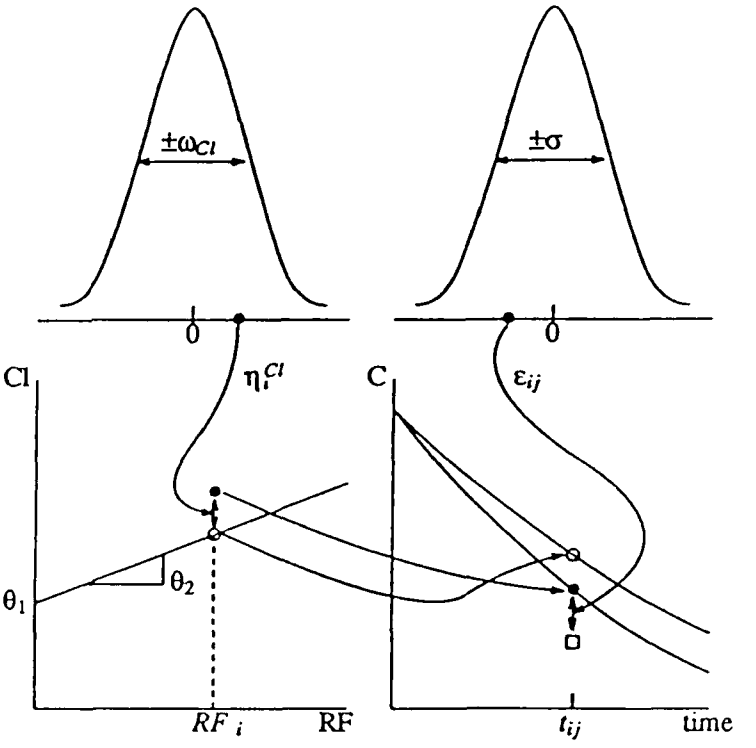

Figure 3. Random and fixed effects influence observations, C_{ij}, from the population point of view. Open circle, lower left, is population parameter predicted clearance, closed circle is true clearance for i^{th} individual which differs from population predicted by $\eta_{Cl,i}$, chosen randomly from a distribution (upper left) with a mean 0 and SD ω_{Cl}. Similarly, lower right, the observed C at time t_{ij} (open square) differs from the true value (closed circle) by an error ϵ_{ij}, chosen independently from a distribution with mean 0 and SD σ_ϵ. The C corresponding to the population-based prediction is also shown (upper curve, open circle) *(Reproduced with permission from reference 14)*

concentration in individual i at time j ($Cp_{i,j}$) to the model predicted plasma concentration ($Cp_{M,i,j}$):

$$Cp_{i,j} = Cp_{M,i,j} + \epsilon_{i,j}$$

Thus a simple population model may now take the form:

$$Cp_{i,j} = DOSE/Vd_i \, e^{-Cli/Vdi * ti,j} + \epsilon_{i,j}$$

$$Cl_i = \theta_1 + \theta_2 * RF + \eta_{Cl,i}$$

$$Vd_i = \theta_3$$

$$var(\eta_{Cl,i}) = \omega^2$$

$$var(\epsilon_{i,j}) = \sigma^2$$

Where:

$Cp_{i,j}$ is the plasma concentration in individual i at time j
Vd_i is the population typical value of Vd
Cl_i is the population typical value of Cl for i's degree of renal function (RF) e.g. Cl_{cr}
$\epsilon_{i,j}$ is the residual random error between i's Cp and the model predicted Cp. $\epsilon_{i,j}$ is normally distributed with a variance of σ^2
θ_1 is the population typical non-renal clearance
θ_2 is the mean proportionality constant relating renal clearance to renal function.
$\eta_{Cl,i}$ is the value of the unexplainable random error in i's clearance. $\eta_{Cl,i}$ is normally distributed with a variance of ω^2

In this example the Vd is not expressed in terms of any covariates nor does it have a random interindividual error model. Thus Vd is assumed not to vary much from individual to individual.

The model is demonstrated graphically in Figure 3.

The most well-known program for applying mixed effects methods is NONMEM (Nonlinear Mixed Effects Modeling) (14). NONMEM analyzes all patient data simultaneously, by the first order approximation method (6,15). It includes models for the three sources of variability described above in the expression for the likelihood of the model. The structural and variance parameters are solved for simultaneously.

Output from NONMEM includes the estimates of means variances and covariances of the parameters. Like other methods, it is a parametric method in

that it assumes a specific (e.g., normal or log-normal) distribution of the pharmacokinetic parameters prior to the estimation. If, prior to any estimations, the population is known to be a "mixture model" (14), with a bimodal distribution of one or more parameters, all of the typical values for distributions corresponding to each mode may be estimated, as well as the fraction of the population belonging to each distribution.

NONMEM is especially useful for sparse, randomly collected data. Although the data are pooled into one data set, the individuals are still identifiable, which permits different numbers of repeated measures for individuals. The inclusion of covariates during the estimation procedure offsets unbalanced data (6). Thus, in contrast to STS, which requires a large number of samples from each individual (a feature which greatly restricts its application), NONMEM is able to derive population models when only a few samples are available from each individual. Consequently, this approach is ideal for studying those populations, such as the very old, very young or very sick, which are most difficult to address using the STS. However, it is important to recognize that although the study design does not call for the collection of samples at specific times, some thought must be given to optimal collection times. For example, a certain pharmacokinetic parameter, e.g. clearance cannot be calculated with any degree of precision unless data are available that reflect the parameter (5). Hence collection of sparse data at non-informative times may result in imprecise estimates.

A comprehensive list of NONMEM-related publications (reviews, methodology and population analyses) through 1994 is available from the NONMEM Project Group (14). In previous investigations NONMEM has performed as well as or, in the case of sparse data, better than traditional methods (8,9,13,16,17,18,19).

However, somewhat biased estimates have been reported (20) especially when the data contain a large amount of random error (21). A modification implemented in the most recent version of NONMEM (v.4) reduces this bias.

Nonparametric Methods

The parametric approach to pharmacokinetics assumes that the pharmacokinetic parameters come from a defined probability distribution (usually normal or lognormal) with unknown parameters (e.g., population typical values and covariance matrix). Both previous methods make this assumption, and utilize a normal or log-normal distribution of parameters in the estimation procedure (6). Nonparametric approaches do not assume any specific underlying distribution of the parameters about the population values, but rather allow for many possible distributions.

Using nonparametric methods, the entire population distribution of each parameter is estimated from the population data. This permits visual inspection of the distribution before, or instead of, committing to one. Population parameters (means, variances, medians, skewness, kurtosis, percentiles, etc.) may be estimated from the distributions. The main advantage of this method is the allowance for non-normal and multimodal distributions, which might occur in a case where a patient characteristic which influences the pharmacokinetics of the drug was overlooked. Inspection of the distribution from the nonparametric approach would reveal the (potentially multimodal) nature of the distribution; whereas with a parametric approach, the form of the distribution is defined prior to any estimations, and the resulting (unimodal) model would be defined by a false mean and an exaggerated variance.

A nonparametric algorithm for estimating population pharmacokinetic parameters which uses a maximum likelihood estimator was introduced by Mallet (Nonparametric Maximum Likelihood (NPML): 22,23). This method permits the use of all forms of distributions, including those containing sharp changes, such as discontinuities and kinks. A consequence of unrestricted inclusion of distributions, with a finite number of patients, is a discrete nature of the probability density function (pdf), where probabilities are assigned to a finite number of parameter values. Another algorithm for this type of estimation which uses expectation maximization as the estimator is Nonparametric Expectation Maximization (NPEM) (24,25). NPEM has been developed as a segment of the USC*PACK collection of programs (26). It includes one and two compartment model capabilities with oral or intravenous dosing. By examining two model parameters at a time, it estimates a joint (3D) pdf over a variable size 2D grid (e.g., a 30 x 30 point grid would produce 900 combinations of values for each pair of parameters), and a marginal density function for each parameter. Equations for calculating the marginal densities from a joint pdf, and the means (expectations), variances, covariances and correlations of the marginal densities for CL and Vd are summarized in the appendix of (10).

When the results of NPEM indicate normal parameter distributions, NPEM and STS give virtually identical estimates of the population pharmacokinetic parameters in the same population (10,11,27). Also, NPEM and STS parameter distributions from the same population produce no apparent difference in predictive performance when used as prior distributions in a Bayesian estimation procedures with patients from a similar population (10,27).

NPEM obviates the need for initial guesses which are required for nonlinear least-squares procedures; however, NPEM is highly dependent on selection of initial

boundaries for the 2D grid base of the joint pdf (10). The case in which NPEM would be preferable to any of the parametric approaches would include an unsuspected multimodal or non-normal distribution of (at least) one of the model parameters. In addition, NPEM is preferable to the traditional methods in the event of sparse data (11,27), as is the case with other direct population PK methods.

Another nonparametric algorithm is the semi- (or smooth-) nonparametric (SNP) method (28). As opposed to NPML and NPEM, SNP places some restrictions on the types of parameter distributions considered, but not to the extent of the parametric methods. The functions which are not permitted are those containing sharp edges or discontinuities, thereby imposing the property of smoothness to the pdf. This is justified since it is likely that the underlying parameter distributions of the population (as opposed to a sample of the population) are smooth. Although the NPML and NPEM distributions are discrete, they may also be smoothed after the estimation procedure is complete (28).

Iterative Two-Stage Method (I2S)

The I2S method may be used with rich data, a mixture of rich and sparse data or only sparse data. To initiate the procedure, an approximate *a priori* population model is required. Sources for these population values may include the literature, the Naive Pooled Data method (discussed above) performed with the current study data and a reasonable choice of parameter variability, or the STS method, providing that considerable informative data are available (29). This population model is used as the set of prior distributions for Bayesian estimation (see Application of Population Pharmacokinetics below) of the individual parameters for all the patients, both rich and sparse in data (Stage 1). The population

parameters are recalculated with these new individual parameters in order to form the new set of prior distributions (Stage 2). The Bayesian estimation step is performed again using the new population model to find more accurate estimates of the individual parameters. This is carried out until the difference between the new and old prior distributions is essentially zero.

Like the STS method, the I2S method yields both individual and population parameters. The method may be performed with any programs supporting Bayesian estimation and least-squares regression, or with the I2S routine (30) which has been implemented in the USC*PACK collection of programs (26).

APPLICATION OF POPULATION PHARMACOKINETICS

In order to discuss the application of pharmacokinetic principles to optimize drug therapy, it is convenient to categorize clinical drug use into two phases, the preapproval drug development phase and the postapproval marketing phase, since each has unique and distinct objectives.

Postapproval - Therapeutic Drug Use

Once a drug is marketed and used for the treatment of a disease or condition, the primary goal is the optimization of the dose for the individual patient. The applicability of the population average dose for an individual will depend on the variability of the pharmacokinetic and pharmacodynamic parameters. If, for a given drug, the variability of the pharmacokinetic parameters within the population is only small, there will be little interindividual variability in the plasma concentrations achieved by a given dose. Thus, providing pharmacodynamic variability is not large, one optimum dose, derived from the

population typical pharmacokinetic parameters would be universally applicable. If on the other hand, pharmacokinetic variability is large, a poor correlation between plasma concentrations and dose will exist. The therapeutic consequence of this will depend on the pharmacodynamic characteristics of both the therapeutic and toxic effects of the drug. Dose individualization is commonly performed on individuals whose pharmacokinetic parameters are most likely to deviate from the population typical values (very old, very young, individuals with renal or hepatic disease) and also for those drugs that possess narrow therapeutic ranges such as aminoglycosides, digoxin, phenytoin, theophylline and cyclosporine (31). In order to truly individualize the dose, the patient's pharmacokinetic parameters are needed.

Traditionally, individual patient parameters are determined using the technique of linear or non-linear least square regression based on two or more blood samples from the patient (32). Numerous examples of this can be found in the literature (33-36). Although straightforward and easy to perform (and still used in many clinical settings) this approach ignores all the previous population studies and bases the determination of an individual's pharmacokinetic parameters on just a few samples.

The Bayesian approach to the determination of individual parameters takes full advantage of both the data from the individual patient and all available information on the population pharmacokinetics of the drug. This concept was first applied to pharmacokinetic determinations in the 1970's (37) and over the last ten years has gained increasing popularity owing to its advantages and the availability of a number of computer programs which make it straightforward and easy to implement (38). In this approach the patient's plasma concentrations and the potential error incurred in their determination are balanced against the

population typical values of the pharmacokinetic parameters and their variability. Specifically, values of the individual pharmacokinetic parameters are chosen so as to minimize the Bayesian objective function below.

$$OBJ_{Bayes} = \sum_{i=1}^{p} \frac{(P_i - \hat{P}_i)^2}{(SD_{P_i})^2} + \sum_{j=1}^{n} \frac{(C_j - \hat{C}_j)^2}{(SD_{C_j})^2}$$

where,

P_i and $\hat{P}_i$ represent population pharmacokinetic parameters and estimates of patient's i=1 to p parameters.

C_j represents the various observed (measured) plasma drug concentrations and $\hat{C}_j$ represents estimates of those concentrations made with the patient's own individualized (fitted) PK model for j=1 to n plasma concentrations

$SD_{P,i}$ and SD_j are standard deviations for the various population parameter values and the observed plasma concentrations respectively.

Several studies using both simulated and real clinical data have validated this approach (39) and demonstrated it to be as good as and in some cases better than the traditional least squares approach. The number of samples available from each patient is an important consideration when comparing the two methods. Studies have shown that as the number of samples increase, the traditional least squares approach begins to out perform the Bayesian approach (40).

The Bayesian regression approach is however dependent on the availability of a comprehensive population model, which must be representative of the patients under study. The direct population approaches of mixed effects modeling and NPEM are particularly well suited for deriving Bayesian *a priori* population estimates (5,12,27,41,24,42,43,44) since these methods can use sparse data, which is frequently all that can be collected from the fragile patients at the extremes of the population. Many examples of the successful application of these

techniques to the individualization of dose can be found in the literature (27,39,42).

Recent efforts have implemented stochastic control of drug therapy. One recent method known as Multiple-Models with Linear dynamics and Quadratic cost (MMLQ) (45) extends the MAP (Maximum A Posteriori)-Bayesian approach to a stochastic framework similar to that for classical engineering, where problems with process noise from multiple sources exist. In this approach, the model is developed to include prior probability density functions, across several "event horizons" (time between measurements), and an ensemble of probabilities can be derived. The subsequent measurements allow for updating model probabilities and open loop control.

Preapproval Phase - Drug Development

During drug development, when a new chemical entity undergoes evaluation for safety and efficacy, the primary goals are to perform the Phase I through III trials in the most efficient manner (46,47). The cost, the period necessary for completion, and the number of patients required for the trials must all be optimized. The role of pharmacokinetics in achieving these goals is well established (46,48,49). Pharmacokinetic studies are used to develop dosage regimens, evaluate dosage requirements of special populations and to investigate potential disease and drug interactions. Even during the preclinical phase, pharmacokinetic studies are necessary in order to establish the validity and support the design of the clinical studies. Several excellent papers on this subject can be found in the literature (46-49). In recent years, regulators and pharmaceutical scientists have promoted an even greater involvement of pharmacokinetics in the drug development process (46).

Specifically a more extensive development and use of pharmacokinetic-pharmacodynamic (PK-PD) models has been advocated, particularly in the early phases of development so that Phase III studies may be performed most efficiently (46,50). This includes taking full advantage of the range of doses studied in dose-tolerance studies, which can provide valuable data on drug concentration-acute toxic effect relationships (46). Additionally, PK-PD models derived from single dose data early in drug development can be extremely valuable in predicting outcomes of other forms of drug administration. These include multiple doses, special patient groups and controlled release formulations (50).

The use of randomized concentration controlled trials (RCCT), where subjects are randomized with respect to plasma concentration rather than dose, has also been promoted (46). Patients' doses are individualized using pharmacokinetic principles to achieve specific predetermined plasma concentrations. The advantage of this approach is that the interpatient variability in response derived from pharmacokinetic variability is eliminated. Thus, the power and the efficiency of the trial increases, which means fewer subjects may be used (51). However, these studies are much more difficult to perform than traditional randomized dose contolled trial (RDCT) and recently, their advantages have been questioned. In theory, RCCT will only be of benefit if pharmacokinetic variability is the major source of interindividual variability in response. For many drugs this may not be the case (52). Additionally, a study, which simulated data using a variety of structural and statistical pharmacodynamic models, found that compared to the simpler RDCT, RCCT offered limited advantages for most models (53). Alternatives of concentration defined, rather than controlled trials, and of effect controlled trials have been advocated (52,54).

Finally, a wider use of the pharmacokinetic screen (55) is being promoted during Phase II and III trials (46). The purpose of the screen is to probe the relationship

between outcome, particularly an unusual one such as unexpected toxicity, and pharmacokinetic variability. The pharmacokinetic screen involves obtaining one to three plasma samples from those individuals who respond to the drug in an unusual manner. Such samples would constitute rich data for the construction of a population pharmacokinetic model and/or evaluating pharmacokinetic versus pharmacodynamic variability.

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