

Willi Weber and Diether Ruppel

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PURPOSE AND RATIONALE

Variability in exposure to a drug leads to variability in the clinical response across a patient population (Rowland et al. 1985). Estimating the variability of the PK (pharmacokinetics) across a patient population requires data obtained from a large study, typically including more than 100 patients. For ethical and practical reasons, pharmacokinetic properties of a drug are difficult to study in large numbers of patients using the traditional approach.

The PPK (population pharmacokinetic) population approach was suggested by Sheiner et al. (1977) for investigating the typical PK of a drug in a large target population using sparse and unbalanced data obtained without any additional cost during routine care of patients. The PPK approach aims to quantitate the effect of various physiologic factors on drug PK with the overall goal of explaining as much variability as possible.

Using the PPK approach in the development of a new drug has the advantage that the relevant pharmacokinetic parameters for a reasonably large population can be obtained from only a few blood samples per subject. The PPK approach is the method of choice in all situations when only sparse and unbalanced data can be obtained. This situation exists when the PK needs to be studied in elderly, critically ill, and pediatric patients, but also very often in preclinical studies investigating the effects of the drug in animals.

Once such a mathematical model is available, the concentration time courses for various scenarios of administration can be predicted. The dosage can be adjusted to achieve a specific clinical goal like drug exposure within the therapeutic concentration window in the whole population or, if necessary, for special

W. Weber • D. Ruppel (✉)
Sanofi Pharma Deutschland GmbH, Industriepark Höchst,
Frankfurt, Germany

subpopulations characterized by their individual physiology. Following the learning and confirming approach (Sheiner 1997), the predicted clinical success for these optimized dose regimens needs to be confirmed in the next clinical study.

The PPK approach estimates the joint distribution of population-specific pharmacokinetic model parameters for a given drug. Fixed effect parameters quantify the relationship, e.g., of clearance to individual physiology like function of liver, kidney, or heart. The volume of distribution is typically related to body size. Random effect parameters quantify the intersubject variability which remains after the fixed effects have been taken into account. Then, the observed concentrations will still be randomly distributed around the concentration time course predicted by the model for an individual subject. This last error term called residual variability needs to be estimated. As fixed and random effects are included, this method is called mixed effects modeling.

The essential features of a population pharmacokinetic study are summarized in a guideline (FDA 1999).

PROCEDURE

The NONMEM (nonlinear mixed effects modeling) software (Beal et al. 1992), mostly used in population pharmacokinetics, was developed at the University of California and is presently distributed by Globomax. For data management, postprocessing, and diagnostic plots, the software S-plus (*Mathsoft*) is frequently used.

Before starting model fitting, all available information obtained in previous studies should be assembled (prior knowledge). The analysis starts with an exploration of the data to generate hypotheses for the model: a statistical summary of demography, plots of the logarithm of the concentration versus time indicate the number of pharmacokinetic compartments involved. With the help of plots of individual time courses in a common coordinate system, subgroups in the population may be identified. Normalizing the curves to unit doses should indicate dose linearity or nonlinearity.

Prior knowledge and various hypotheses are condensed into models. NONMEM determines the parameter vector including fixed and random effects of each model using the maximum likelihood algorithm. NONMEM uses each model to predict the observed

data set and selects the best PPK parameter vector minimizing the deviation between model prediction and observed data. Comparing model fits by the criteria discussed in the section "Evaluation" should decide which hypothesis is the most likely. As a general rule, the model should be as simple as possible, and the number of parameters should be at a minimum.

The situation after an IV bolus for a system described by a one compartment model with first order elimination can serve to illustrate the procedure. The observed concentration $c_{i,j}$ of an individual i at the time t_j can be modeled as

$$c_{i,j} = \left(\frac{\text{Dose}}{V_i} \right) e^{-k_i t_j} + \epsilon_{i,j}; \quad \epsilon_{i,j} \sim N(0, \sigma^2) \quad (46.1)$$

with $k_i = \frac{CL_i}{V_i}$, where CL_i and V_i are the individual clearance and the individual volume of subject i . $\epsilon_{i,j}$ is the residual error drawn from a normal distribution with zero mean and variance σ^2 (covariance matrix describing the within subject or residual variability), the intraindividual variability.

The pharmacokinetic parameters themselves are modeled like

$$CL_i = \theta_{CL} e^{\eta_{CL_i}}; \quad \eta_{CL_i} \sim N(0, \omega^2), \quad (46.2)$$

where θ_{CL} is a population mean clearance and η_{CL_i} is again a random variable representing the deviation from the population mean of the clearance for the i -th subject. η_{CL_i} is normally distributed with zero mean and variance ω^2 (covariance matrix describing the between subject variability). The unexplained intersubject variability acts as random effect η_{CL_i} on the clearance.

It is important to emphasize that all pharmacokinetic, fixed effect, and random parameters, i.e., θ , ω^2 , and σ^2 , are fitted in one step as mean values with standard error by NONMEM. A covariance matrix of the random effects can be calculated. For a detailed description of the procedure, see Grasela and Sheiner (1991) and Sheiner and Grasela (1991).

In a subsequent step, the modeler tries to explain part of the unexplained interindividual variability. Fitted individual parameters (or the variable part expressed by η) are plotted against physiological parameters like weight or indicators of renal or metabolic functionality. Identified dependencies should

enter into the model. For example, clearance is very often modeled as depending on the covariate CL_{CR} (creatinine clearance):

$$CL_i = \theta_{CL} \left(\frac{CL_{CR_i}}{4L/h} \right)^{\theta_{CL_{CR}}} e^{\eta_{CL_i}}. \quad (46.3)$$

In this equation, CL_{CR_i} is the actual creatinine clearance of subject i . The fixed effect parameters are now θ_{CL} corresponding to the clearance of a person with a CL_{CR} of 4 l/h and $\theta_{CL_{CR}}$ as an exponent describing the increase of CL_i with CL_{CR} .

The relevance of CL_{CR} for clearance is tested using the likelihood ratio test (Beal et al. 1992). The so-called full model 1 (alternative hypothesis) given in Eq. 46.3 is tested against the reduced model with $\theta_{CL_{CR}} = 0$ (null hypothesis) characterized by Eq. 46.2.

The more complex full model is accepted only if the objective function obtained with the full model is more favorable than the objective function obtained with the reduced model (see "Evaluation").

Concentration time courses can be simulated by the model and the demographic parameters for different dose regimens. The final administration of the drug has to be adjusted so that, e.g., 95% of the target population falls into the therapeutic window. If subpopulations differ too much, adjusted administration regimens have to be considered.

EVALUATION

The following criteria determine about the best model:

1. The OF (objective function: negative log of probability, $-2 \ln(\text{Prob})$), calculated by NONMEM, is a measure for the deviation between the model prediction and the observed data. It enters into the likelihood ratio test as follows: if the OF of the full model minus the OF of the reduced model is smaller than -3.84 , then the full model can be accepted at a significance level of $p < 0.05$ (Beal et al. 1992).
2. The observed concentrations plotted against the predicted concentrations had to be more randomly distributed around the line of unity.
3. The weighted residuals and the individual residuals plotted against the predicted concentrations had to show the most symmetric distribution around zero.

In order to validate the final model, the data set can be split randomly into two parts. The model is

developed with one part, the index data set. With this model and the demographic data of the second part, the validation data set, observations for the validation data set can be predicted. The difference of predicted data and observations is a measure of the accuracy of the model. An alternative is the bootstrap method (Efron 1981).

MODIFICATION OF THE METHOD

Data from individuals drawn from a target population are not completely independent. Concentration time curves (longitudinal data) of a subject are considered to be driven by a functionality depending on individual parameter values. But what is the connection between the same parameters in different persons? Parts of it may be described by a functionality depending on demographic variables. In any case, unexplained intra- and interindividual random effects remain. Mixed effect modeling clearly distinguishes between these two sources of randomness.

Modifications of the method differ in the way they deal with these different levels of random effects, i.e., how they distribute or confound them. It should be noted that the different handling of random effects has also consequences for the fixed effects.

1. In a situation with many data from each individual drawn in an intersubject balanced manner, a two-stage method is very often used: each individual is fitted individually without considering the interindividual dependencies. In a second step, the parameters are resumed as population mean and standard deviation, often considered as interindividual variability. (STS (standard two-stage method), (Steimer et al. 1985)).
2. If only a few data per subject are available, they are sometimes pooled and considered as coming from one hyperanimal. If several observations are available at the same time, they are averaged, and means and standard deviations can be calculated. In a second step, the mean values are fitted to a pharmacokinetic model. (NAD (naive averaging data method) (Steimer et al. 1985)). A different naive technique is the NPD (naive pooled data) method proposed by Sheiner (Sheiner and Beal 1980). Again, all data are pooled but fitted in one step to a pharmacokinetic model. In both cases, intra- and interindividual random effects are confounded. An influence of covariates cannot be determined by this approach.

3. Mixed effect modeling deals with the situation in between. Inter- and intraindividual variabilities are separated and calculated within the same step. Interindividual random effects are calculated for those parameters for which this information can be drawn from the data set. In general, only one residual error is calculated. The method is very well suited for sparse and unbalanced data situations.

Population pharmacokinetics can be extended to pharmacodynamics and PK/PD modeling using a link model like an effect compartment (Sheiner et al. 1979). In huge clinical trials, only a limited number of patients can be included in a pharmacokinetic satellite study. The model is developed in this satellite. Knowing the demographic covariates of the patients in the whole study, concentration time curves and even effect time curves can be predicted.

Alternative software like NPEM uses nonparametric procedures for the statistical part of the models (Jelliffe et al. 1990).

CRITICAL ASSESSMENT OF THE METHOD

The NAD and NPD methods confound several sources of variability and very often give biased estimates of the mean values of the pharmacokinetic parameters (Steimer et al. 1985). But when the population is very homogeneous, the naive approaches already give reasonable results. The widespread STS method requires the estimation of a large number of parameters, reducing the degree of freedom and leading to over parameterization (large SEMs).

Mixed effect modeling is a very flexible one-step method. It can cope with many situations. It is the only method which can deal with sparse data and unbalanced data sparse situations. The method can start in preclinical phases with animal data. In phase I with a homogeneous population and many observations per individual, the structural model, dose linearity, and bioavailability are determined. In phase II and phase III, patients are investigated, and the demographic parameters should spread over a large range in order to determine the variability in the target population. The method is well suited to perform meta-analysis of several studies.

It should be emphasized that models are not the truth and that different models can describe the same data with the same accuracy. Whereas interpolation for

doses or covariates is in general possible, extrapolations should be considered with care. Extrapolation with different models, if available, can give a feeling about the range for the observations to be expected.

Simulations should be used for the design of the next experiment (trial). The new observations should be compared to the prediction allowing improvement of the model in an iterative manner (Sheiner 1997).

EXAMPLE

Introduction

Levofloxacin is the l-isomer of the racemate ofloxacin, a quinolone antibacterial agent used worldwide to treat a wide range of infections. The PK profile of levofloxacin was first characterized in healthy volunteers. The following prior knowledge was obtained before the clinical study presented below. Levofloxacin is primarily excreted renally. Increasing doses of levofloxacin showed linear PK over the investigated dose range between 50 and 600 mg. The PPK of levofloxacin used in patients with respiratory tract infections was investigated by Tanigawara et al. (1995).

Objective

Can 500-mg levofloxacin given twice daily achieve the therapeutic goal of plasma levels above 2 mg/l, the MIC (minimum inhibitory concentration) in male and in female patients?

Materials and Methods

The PPK were analyzed in a subpopulation of 44 out of 314 patients with pneumonia being treated with levofloxacin. Patients received two daily doses of 500 mg for 10 to 15 days. Initially, the drug was given intravenously as an infusion for approximately 60 min. The switch from IV to oral treatment was suggested after a minimum of four IV doses. Three to five blood samples were taken from each patient, 199 blood samples in total.

The available concentration time data is typical for a clinical study: there are relatively few observations on each of a large number of patients, and samples are not taken at the same time points (sparse and unbalanced data). Neither the NAD method nor the STS method can be used. A one compartment model with absorption compartment and first order elimination was fitted to the data by mixed effect modeling with

NONMEM. Clearance and volume of distribution were described by

$$CL_i = \theta_{CL} \left(\frac{CL_{CR_i}}{4L/h} \right) e^{\eta_{CL_i}} \quad (46.4)$$

(Eq. 46.3 with $\theta_{CL_{CR}} = 1$)

$$V_i = \theta_V \left(\frac{WT_i}{70 \text{ kg}} \right) (1 + (2 - SEX_i)\theta_{SEX}) e^{\eta_{V_i}}. \quad (46.5)$$

The model uses CL_{CR} , WT (body weight [kg]), and SEX (1 = male and 2 = female) as covariates.

Alternatively, the volume model was simplified using LBM (lean body mass in kg) instead of WT and SEX. LBM is related to WT, HT (height in cm), and SEX in the following equation:

$$\begin{aligned} \text{LBM} & \begin{pmatrix} \text{male} \\ \text{female} \end{pmatrix} \\ & = \begin{pmatrix} 1.1 \\ 1.07 \end{pmatrix} \text{WT} - \begin{pmatrix} 128 \\ 148 \end{pmatrix} \left(\frac{\text{WT cm}}{\text{HT kg}} \right)^2 \text{ kg}. \end{aligned} \quad (46.6)$$

The model for V (volume of distribution) given as

$$V_i = \theta_V \left(\frac{\text{LBM}_i}{50\text{kg}} \right) e^{\eta_{V_i}} \quad (46.7)$$

needs one parameter, θ_{SEX} , less than the model given in Eq. 46.5. Now, the PPK model uses in total only two covariates, i.e., CL_{CR} and LBM.

RESULTS

PK Differences Between Male and Female Patients?

The volume given in Eq. 46.5 as a full model (A) changes with $\theta_{SEX} = 0$ to a reduced model reduced model (B). To perform the likelihood ratio test, both models were fitted with NONMEM, and the OF of the full model (A) was 6.39 points lower than the OF obtained for the reduced model (B). This difference is highly significant, so the full model (A) is preferred when compared to a reduced model (B).

WT and SEX are combined in LBM. To simplify the model, we described the fixed effect on V only with LBM as a single measure of body size. Using Eq. 46.7

Table 46.1 PK parameters from mixed effect modeling using Eqs. 46.4 and 46.7. The absorption coefficient θ_{KA} was fixed to 1/h

	Parameter	Mean	SEM
Fixed effects θ	θ_{CL} [l/h]	5.3	0.3
	θ_V [l]	76	5
	θ_{KA} [1/h]	1	fix
Random effects ω^2	ω_{CL}^2	0.12	0.02
	ω_V^2	0.11	0.04
Residual error σ^2	σ^2	0.03	0.01

in model (C), we repeated the NONMEM fit and compared the OF obtained for model (C) with the previous two fits. Model (A) was still 3.1 points better than model (C). We preferred model (C) because it uses only body size while model (A) uses body size and sex as demographic covariates in the V model. Table 46.1 resumes the values of the PPK parameter vector including θ (vector of parameter, describing the fixed effect model), ω^2 , and σ^2 calculated for model (C).

Concentration time curves for three individuals with different kidney functions CL_{CR} are shown in Fig. 46.1. The broken lines CL_{CR} represent the time-dependent CL_{CR} as a measure of the kidney function. For the subject shown in the center panel, the CL_{CR} decreases at 3.5 days causing a steep increase in the drug concentration. Dots are observations CONC (observed concentration), and full lines PRED (model predictions for the population with $\eta = 0$) correspond to the model predictions for a typical individual with a specific set of mean covariates CL_{CR} , WT, and SEX (fixed effects). The broken lines IPRE (model predictions for the individual subject with random η_i) are the individual predictions for the subject taking the random effects on volume and clearance into account.

Once the model is in place, simulations can be performed in order to find or to verify the optimal dose regimen.

In Fig. 46.2, mean C_{ss} (concentration at steady state), given in Eq. 46.8, as a function of CL_{CR} is shown.

$$C_{ss,i} = \frac{\text{dose rate}}{CL_i} \quad (46.8)$$

The circles correspond to the observations. The lines are calculated using the fit parameters and Eq. 46.2 for the 2.5%, 50%, and 97.5% quantiles. All

Fig. 46.1 Individual concentration time courses. *CONC* creatinine clearance; *PRED* model predictions for the population with $\eta = 0$; *IPRE* model predictions for the individual subject with random η_i ; *CL_{CR}* creatinine clearance in l/h is calculated as left-hand scale *10/4

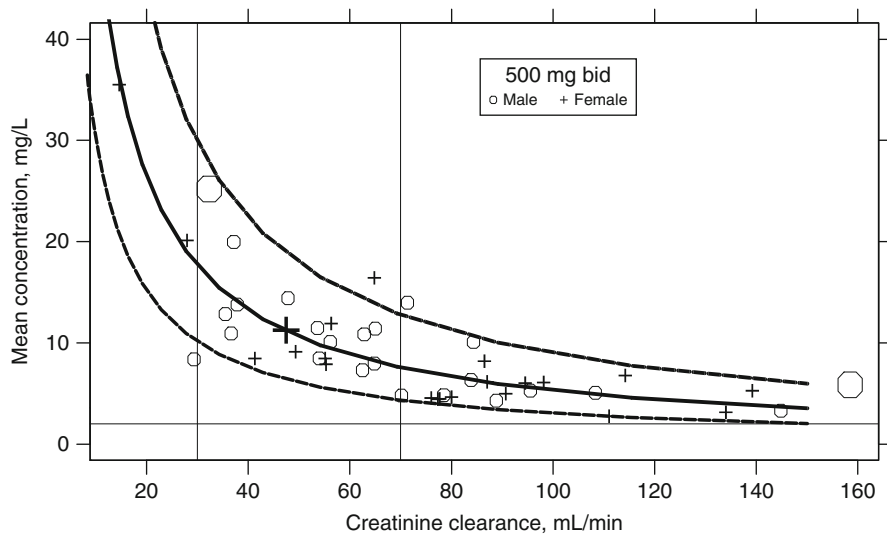
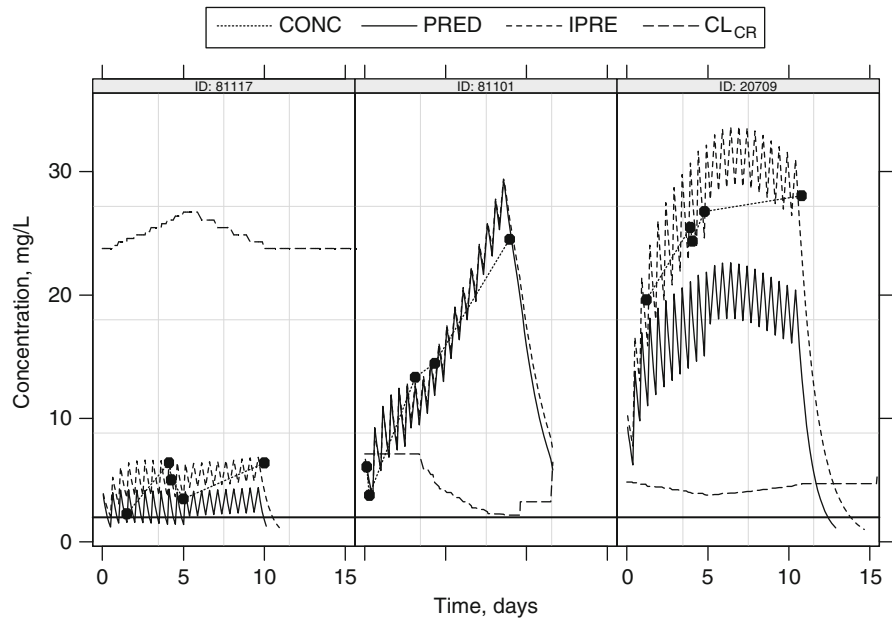


Fig. 46.2 Mean concentrations at steady state after twice daily 500-mg levofloxacin. The circles and crosses correspondent to the individual CL estimates in male and female patients, respectively. Three filled circles correspond to patients which PK is shown in Fig. 46.1. The lines are calculated using the fit

parameters given in Table 46.1 and Eq. 46.2 for the 2.5, 50, and 97.5% quantiles. All except two individuals are within these limits. The vertical solid lines mark patients with creatinine clearances of 30 ml/min and 70 ml/min, curves stop at 150 ml/min

except two individuals are within these limits. As reveals from Fig. 46.2, the selected dose regimen of 500 mg twice daily achieves even in more than 95% of male and female patients with normal kidney function C_{ss} concentrations above the MIC of 2 mg/l.

Figure 46.3 shows the joint distribution of V and CL_{tot} (total clearance) for males and females as calculated by the model (C). Volume and clearance are distributed around mean values (center of the ellipse), and they are slightly correlated to

Fig. 46.3 Joint distribution of V and CL_{tot} . Ellipse joint 95% prediction interval in a subpopulation of male patients ($CLCR = 72.53$ ml/min and $LBM = 57.63$ kg) and in a subpopulation of female patients (58.32 ml/min and 43.12 kg). The individual V and CL_{tot} estimates calculated by NONMEM are grouped according to the degree of renal failure

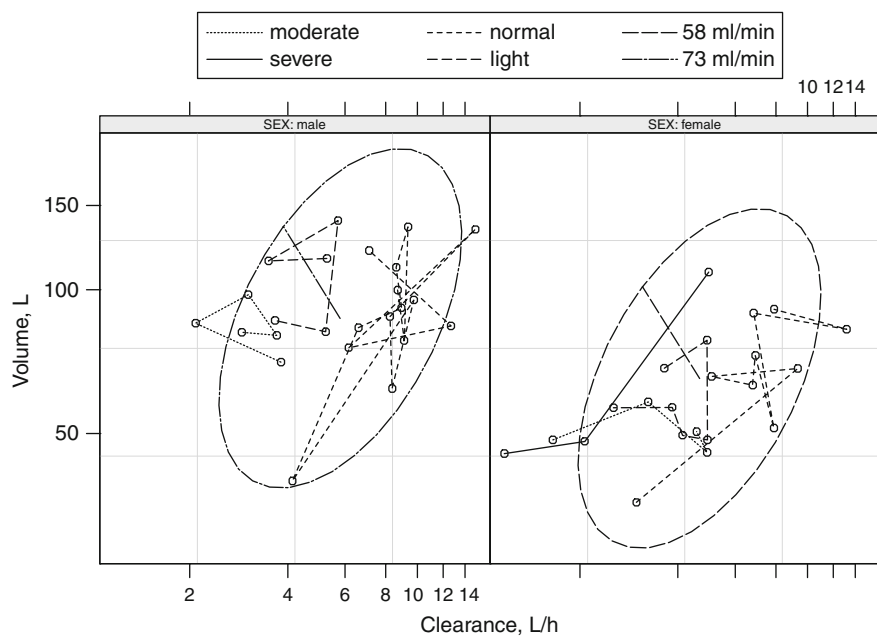
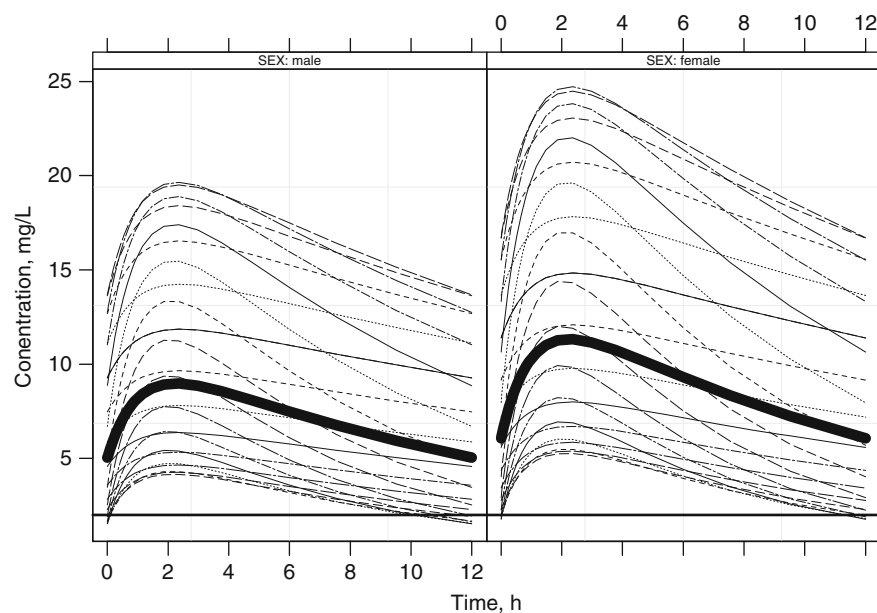


Fig. 46.4 Simulations of the concentration time course under steady state conditions as predicted by the model (C) for a 500-mg twice daily dose regimen. The broad line corresponds to the typical male ($CLCR = 72.53$ ml/min and $LBM = 57.63$ kg) and female (58.32 ml/min and 43.12 kg) patients. All other lines are calculated using only CL and V pairs of the 95% contour line of their joint probability of occurrence as shown in Fig. 46.3 as ellipses. The horizontal solid line marks the MIC of 2 mg/l



each other. The 95% contour line of their joint probability of occurrence is shown as ellipses for male and female.

Simulations of the concentration time course under steady state conditions as predicted by the model for a 500-mg twice daily dose regimen are shown in Fig. 46.4. The broad line corresponds to the typical

male and female patients. All other lines are calculated using only CL and V pairs of the 95% contour line of their joint probability of occurrence as shown in Fig. 46.3 as ellipses. As reveals from Fig. 46.4, concentration time courses remain within an interval describing the concentrations expected in 95% of

DISCUSSION

The PPK approach uses all the data observed at all sampling times and from all subjects enrolled in the satellite study in a single step to extract the information necessary to optimize a dose regimen.

For the example of levofloxacin given twice daily 500 mg, 95% of male and female patients achieved the therapeutic goal and showed concentrations above 2 mg/l (MIC) for more than 10 hours of the 12-h dose interval. Due to their smaller volume of distribution, peak concentrations are higher, and half-lives are shorter in female patients. The different extents of accumulation as an effect of differences in half-lives become evident when comparing the through levels. The highest concentrations reached are still below the safety limits. Therefore, the same dose regimen for male and female patients was recommended.

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