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Population Pharmacokinetic Study of Isepamicin with Intensive Care Unit Patients

MICHEL TOD,[1]* CHRISTOPHE PADOIN,[1] CATHERINE MINOZZI,[2] JEAN COUGNARD,[2] AND OLIVIER PETITJEAN[1]

Département de Pharmacotoxicologie, Hôpital Avicenne, 93009 Bobigny Cedex,[1] and Schering-Plough, Levallois-Perret,[2] France

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The pharmacokinetics (PK) of isepamicin, a new aminoglycoside, were studied in 85 intensive care unit (ICU) patients and were compared with those observed in 10 healthy volunteers. A parametric method based on a nonlinear mixed-effect model was used to assess population PK. Isepamicin was given intravenously over 0.5 h at dosages of 15 mg/kg once daily or 7.5 mg/kg twice daily. The data were fitted to a bicompartmental open model. Compared with healthy volunteers, the mean values of the PK parameters were profoundly modified in ICU patients: elimination clearance was reduced by 48%, the volume of distribution in the central compartment (V_c) was increased by 50%, the peripheral volume of distribution was 70% higher, the distribution clearance was 146% lower, and the elimination half-life was ca. 3.4 times higher. The interindividual variability in PK parameters was about 50% in ICU patients. Five covariates (body weight [BW], simplified acute physiology score [SAPS], temperature, serum creatinine level, and creatinine clearance [CL_{CR}]) were tentatively correlated with PK parameters by multivariate linear regression analysis with stepwise addition and deletion. The variability of isepamicin clearance was explained by three covariates (BW, SAPS, and CL_{CR}), that of V_c was explained by BW and SAPS, and that of the elimination half-life was explained by CL_{CR} and SAPS. Simulation of the concentration-versus-time profile for 500 individuals showed that the mean peak (0.75 h) concentration was 18% lower in ICU patients than in healthy volunteers and that the range in ICU patients was very broad (28.4 to 95.4 mg/liter). Therefore, monitoring of the isepamicin concentration is in ICU patients is mandatory.

Isepamicin is a new semisynthetic aminoglycoside derived from gentamicin B whose resistance to aminoglycoside-inactivating enzymes is better than that of all the other available members of this family of antibiotics (5, 20). Its pharmacokinetics (PK) have been studied in healthy volunteers (21), in patients with various degrees of renal insufficiency (7, 24) or end-stage renal disease (8), and in children (11). Isepamicin PK were very similar to those of all of the other aminoglycosides related to gentamicin (13).

Aminoglycoside PK are known to be more or less modified in intensive care unit (ICU) patients (1, 9, 26). The volume of distribution (V) has been shown to be higher than usual (18), whereas elimination clearance (CL) is lower (16), but isepamicin has not been studied in this population. Therefore, the aim of the study described here was to compare the PK of isepamicin in 85 ICU patients with those in 10 healthy volunteers. Because only a few datum points per patients were available, a nonlinear mixed-effect model approach was used to estimate the population PK parameter values of isepamicin and to look for their relationships with several demographic and biological covariables (14, 23).

MATERIALS AND METHODS

Patients. Eighty-five ICU patients were included in the study. Major demographic, clinical, and biological data for this population are summarized in Table 1. Patients were enrolled if they had severe nosocomial pneumonia, were over 18 years of age, were intubated and receiving mechanical ventilation, were in an ICU for more than 3 days, and had a simplified acute physiology score (SAPS) of between 10 and 25 at the time of admission to the ICU. The infection was substantiated by the presence of purulent tracheobronchial secretions, a chest X-ray-documented infiltrate(s), and a 25% or more increase in leukocyte count.

Healthy volunteers. The data from the study by J. M. Herron (10) were used. The demographic data for the 10 healthy volunteers retained as the control group are summarized in Table 1.

Administration of drug (patients). Patients were randomly assigned to receive isepamicin (Schering-Plough, Levallois-Perret, France) infused intravenously over 0.5 h. In the first group, 42 patients received isepamicin 15 mg/kg of body weight once daily; in the second group, 43 patients received isepamicin 7.5 mg/kg twice daily. Ceftazidime or imipenem was systematically combined with isepamicin.

Blood samples were taken at 0.75 h (i.e., 0.25 h after the end of the infusion) and at 12 h (second group) or 24 h (first group) to measure the peak and trough concentrations after one or several infusions. The subjects received 2 to 25 isepamicin administrations, and the mean ± standard deviation (SD) number of samples per subject was 5 ± 3, with a median of 4. The total number of samples

TABLE 1. Characteristics of the 85 ICU patients and the 10 healthy volunteers

Group and value	Age (yrs)	Wt (kg)	Serum creatinine concn (mg/dl)	CL_{CR} (ml/min)	SAPS	Temp (°C)
ICU patients						
Mean	59.1	65.3	1.08	80	13.9	38.9
Median	63	65	0.94	69	14	39
SD	17.1	11.6	0.53	42	2.8	0.94
Minimum	21	41.4	0.30	19	10	34.8
Maximum	87	100	2.89	199	22	40.6
Healthy volunteers						
Mean	31.4	85.8	1.03	123		
Median	32.5	84.5	0.97	127		
SD	5.0	13.2	0.07	25.2		
Minimum	19.0	69.5	0.95	94		
Maximum	37.0	107.5	1.20	164		

* Corresponding author. Mailing address: Département de Pharmacotoxicologie, Hôpital Avicenne, 125, route de Stalingrad, 93009 Bobigny Cedex, France.

TABLE 2. Validation criteria for the population analyses

Group	No. of outliers	Standardized residuals								KS test[c]
		No. of datum points	Mean	Median	SEM	CI_{95}[a]	Minimum	Maximum	P[b]	
Healthy volunteers	0	154	0.003	−0.116	0.071	−0.135–0.141	−2.09	2.62	0.966	0.100 (NS[d])
ICU patients	4	444	−0.158	−0.186	0.037	−0.230–−0.086	−2.99	2.40	0.001	0.174 (NS)
Healthy volunteers + ICU patients[e]	3	598	−0.081	−0.087	0.028	−0.137–−0.026	−2.75	2.70	0.004	0.187 (NS)

[a] CI_{95} 95% confidence interval of the mean.
[b] t test to compare the mean to zero.
[c] KS test, Kolmogorov-Smirnov test to compare the distribution of standardized residuals to N (0, 1).
[d] NS, not significant.
[e] After taking into account the covariates in the population model.

was 448. Plasma was separated and was immediately stored at −20°C until the determination of the isepamicin concentration.

Administration of drug (healthy volunteers). Of the 18 subjects in the original study the 10 subjects who received isepamicin once daily (0.5-h intravenous infusion) were retained. The isepamicin dose varied between 495 and 1,260 mg. Only the data from the first administration were used, i.e., 16 samples per subject taken at the following times: 0.17, 0.33, 0.5, 0.53, 0.58, 0.67, 0.83, 1, 1.5, 2.5, 3.5, 4.5, 6.5, 8.5, 12.5, and 24.5 h after the start of the infusion.

Drug assay. Isepamicin concentrations in plasma from patients were measured by immunopolarization of fluorescence (TDX; Abbott, Rungis, France). The limit of quantification was 0.4 mg/liter. Interrun reproducibilities were 3.7% at 5 mg/liter, 2.5% at 15 mg/liter, and 1.8% at 25 mg/liter. Isepamicin concentrations in plasma from healthy volunteers were measured by high-performance liquid chromatography by a method similar to that given previously (15). Briefly, the procedure involved plasma deproteinization with ethanol-methylene chloride, centrifugation, and injection of the supernatant. An automated column-switching technique was used in a system with two columns. The first column (10-μm Cyano; 4 by 4 mm) was used to extract isepamicin and the internal standard (dibekacin). The second column (5-μm C18; 4.6 by 150 mm) was used to separate isepamicin from dibekacin and other substances. The isepamicin in the effluent was quantitated by on-line derivatization with orthophthalaldehyde and fluorescence detection. The limit of quantification was 0.1 mg/liter. Interrun reproducibilities were 7.4% at 0.1 mg/liter, 1.9% at 5 mg/liter, 6% at 10 mg/liter, and 7.8% at 50 mg/liter.

Data analysis. The concentration-versus-time data for isepamicin in plasma were analyzed by a nonlinear mixed-effect modeling approach. An open two-compartment PK model with zero-order input was used to describe isepamicin kinetics. This choice was based on previous studies on the disposition of isepamicin (7). The four-dimensional vector of kinetic parameters consisted of the volume of distribution in the central compartment (V_c), CL, the distribution clearance (CL_D), which describes the exchange between the central and the peripheral compartments, and the volume of the peripheral compartment (V_t). The model was implemented as a set of two differential equations, enabling the computation of the isepamicin concentration at any time for any given dosing regimen (25). In order to obtain a population estimate of the elimination half-life ($t_{1/2}$), which is a key parameter for clinical use, the data were also analyzed by fitting them to a bicompartmental model implemented as the usual integrated equation (25), with the slope of the terminal phase (β) replaced by (log 2)/$t_{1/2}$. Measurement errors for levels in plasma were assumed to be additive, independent, and Gaussian, with a mean of zero and with variance proportional to the concentration. These choices were justified by the pattern of the analytical precision in each study.

The distribution of each PK parameter in the population was assumed to follow a log-normal distribution. Covariances were assumed to be zero.

The population characteristics of the PK parameters (i.e., means and variances) were calculated by a parametric method based on an expectation-minimization algorithm (18). The method is implemented in the P-PHARM software (version 1.3; Simed, Créteil, France). A detailed description of the principles of the algorithm are given in the Appendix. Individual parameter values were then computed by the Bayes method as the maximum of the posterior probability density function of the parameters, given the concentrations measured in each subject.

Also, correlations of the (posterior) PK parameters with several covariables measured on the first day of isepamicin administration (age, weight, temperature, SAPS, the inverse of the serum creatinine level, and creatinine clearance [CL_{CR}]) were analyzed by multivariate linear regression with step-by-step inclusion and deletion of covariates (18). The threshold value of the F statistic (mean square associated with adding or removing a covariate x_j in the regression equation/mean square residual for equation containing covariate $x_1 \ldots x_j$) was 5 for inclusion or deletion. After identification of the pertinent covariables, the data were reanalyzed to determine the population characteristics of the PK parameters when the covariables were taken into account.

The population data fitting was validated by several criteria (6, 18): (i) visual examination of the goodness of fit of each individual concentration-versus-time curve compared with the experimental data; (ii) comparison of the mean of the standardized residuals to zero by Student's t test; (iii) comparison of the cumulative distribution of the standardized residuals to that of a normal distribution with a mean of zero and a variance of one by using the Kolmogorov-Smirnov test; (iv) application of the t test for the detection of outliers; a predefined level of not more than 2% outliers of the total number of points was considered a criterion of validation; (v) visual comparison of the distribution of the posterior estimates of the PK parameters with the log-normal distribution; and (vi) for the inclusion of covariates, the interindividual variability of the parameters had to be reduced and the maximum likelihood of the data had to be increased.

Four population analyses were made: (i) analysis of the reference population, i.e., 10 healthy volunteers; (ii and iii) analysis of all of the data for the 85 ICU patients by using the two alternative parameterizations of the PK model in order to evaluate the incidence of this pathological situation on isepamicin kinetics, by comparison with the results for healthy volunteers; and (iv) analysis of the data for all the subjects (85 patients plus 10 healthy volunteers) in order to look for correlations between PK parameters and covariates. In healthy volunteers, temperature was assumed to be 37°C, SAPS was set at 1, and CL_{CR} was calculated by the method of Cockroft and Gault (2).

Simulations. The population PK parameter values of isepamicin were used to generate simulations of the mean ± SD concentrations in healthy volunteers and ICU patients. Three 15-mg/kg infusions over 0.5 h were assumed to be given to a population of 500 subjects, with a between-dose interval of 24 h, and the concentrations at 0.75, 24, 48.75, and 72 h were calculated. The population model obtained in the analysis of all subjects (85 patients plus 10 healthy volunteers) after taking into account the pertinent covariates (weight, SAPS, CL_{CR}) was used for the simulation. Weight and SAPS were assumed to follow a normal distribution, while CL_{CR} was assumed to follow a log-normal distribution, with mean and SD as described in Table 1 for each population (healthy or ICU subjects). The homemade POPSIM software was used for this purpose (a description is provided in the Appendix).

RESULTS

Validation. The validation criteria for the two majors analyses are given in Table 2. The number of outliers, less than 2% of the total number of points, was very small. The Kolmogorov-Smirnov test indicated that the cumulative distribution of the

TABLE 3. Population pharmacokinetic parameters in the two populations

Group	Value	CL (liters/h)	V_c (liters)	CL_D (liters/h)	V_t (liters)	$t_{1/2\beta}$ (h)
Healthy volunteers	Median	5.33	8.75	5.94	4.85	2.22
	Mean	5.62	9.37	7.50	5.44	2.23
	SD	1.86	3.60	5.77	2.76	0.20
	% CV[a]	33	38	77	51	9
ICU patients	Median	2.78	13.1	2.41	8.25	7.55
	Mean	3.18	14.6	2.82	12.6	8.41
	SD	1.76	7.1	1.71	14.5	4.13
	% CV	55	49	61	115	49

[a] CV, coefficient of variation.

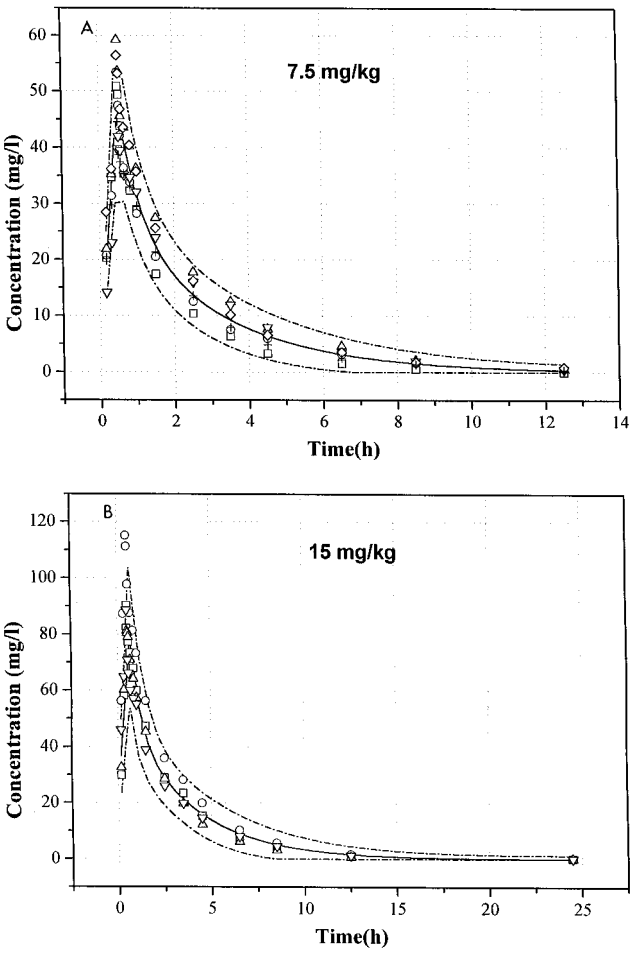

FIG. 1. Mean isepamicin population model curves with 95% confidence intervals in healthy volunteers after the administration of 7.5 mg/kg ($n = 6$) (A) or 15 mg/kg ($n = 4$) (B). Each symbol represents a separate subject.

standardized residual was not significantly different from that of normal distribution N (0, 1). However, the mean of the standardized residual in ICU patients was slightly less than zero, and the difference was significant. Although the magnitude of the difference was small, its existence indicated some minor model misspecification. Although it is well-known that the kinetics of aminoglycosides are triexponential (12), we used a biexponential model, which could explain part of the bias, because no convergence could be obtained when a triexponential model was used to fit the data, probably because there was very little information about the parameters of such a model in the ICU population data (i.e., samples other than those containing peak and trough concentrations should have been drawn). For practical purposes, the bias introduced by a bicompartmental model is very small, and therefore, the population analysis was considered to be validated.

Population PK parameter values. The population PK parameter values for healthy volunteers and ICU patients are summarized in Table 3, and the population curves are shown in Fig. 1. The values of the key parameters $t_{1/2}$ and the volume of distribution at steady-state (V_{ss}), which is the sum of V_c and V_t, of isepamicin in healthy volunteers were found to be very similar to those of other aminoglycosides, i.e., V_{ss} was ca. 0.2 liters/kg and $t_{1/2}$ was ca. 2 to 3 h (13). Profound modifications of all median PK parameter values were observed in ICU patients: CL was reduced by 48%, V_c was increased by 50%, CL_D was reduced by 146%, and V_t was increased by 70%. Overall, the $t_{1/2}$ was ca. 3.4 times higher in ICU patients. The interindividual variability in PK parameter values in ICU patients was about 50% for all parameters but amounted to 115% for V_t.

Analysis of covariates. The contribution of each of the five covariates to the explanation of the interindividual variability of isepamicin PK parameters is summarized in Table 4. The coefficients of the linear regression model between each PK parameter and the pertinent covariates are given in Table 5.

These relationships can be used to calculate the mathematical expectation of the isepamicin PK parameter values in an individual given their covariates. Taking V_t as an example, the covariate model is as follows: $V_t = 0.397 \times \text{SAPS} + 4.01$. The expected value of V_t in a patient with a SAPS of 10 is 7.98 liters.

Simulation studies. The simulated peak and trough concentrations of isepamicin in both populations are described in Table 6. These simulated concentrations must be compared with the experimental mean ± SD isepamicin concentration after the first administration of a 15-mg/kg dose to the ICU patients: 61 ± 30 mg/liter (peak) and 2.9 ± 5.0 mg/liter (trough). The means of the experimental concentrations versus the simulated concentrations are very similar, but the SDs of the experimental concentrations are much larger than the SDs of the simulated ones. This discrepancy results in part from the fact that the simulation does not account for measurement error and sampling time error, thereby underestimating the experimental variability.

DISCUSSION

The modifications of isepamicin PK parameter values in ICU patients compared with those in healthy volunteers are qualitatively similar to those observed with other aminoglycosides (1, 9, 16, 17, 26). In one study, the increase in the volume of distribution (V_β) of amikacin was linearly related to the severity of illness, as measured by the APACHE II score (17). The high V_β in these patients has been explained by the increased volume of extracellular fluids resulting from diffuse microcirculatory injury with endothelial damage and tissue edema induced by sepsis. Indeed, Fuhs et al. (4) showed that the V_β of aminoglycosides decreased during treatment of the infection, with changes of more than 1 liter in 83% and changes of more than 5 liters in 48% of the intrapatient comparisons. The CL of drugs may vary in ICU patients because severe illness is accompanied by modification of cardiac output and systemic vascular resistance, the patient is febrile and catabolic, and total serum protein and albumin levels decrease, while α_1-acid glycoprotein levels increase. Therefore, the CL

TABLE 4. P Variability in PK parameter values explained by the covariates

Parameter	% Variability (partial F value of ANOVA[a])				
	CL	V_c	CL_D	V_t	$t_{1/2\beta}$
Wt	38 (52)	14 (25)			
CL_{CR}	11 (30)				36 (42)
SAPS	18 (30)	15 (18)	75 (278)	25 (31)	13 (23)
Temperature					
1/Serum creatinine level					
Total	67	29	75	25	49

[a] ANOVA, analysis of variance.

TABLE 5. Coefficients of the linear regression model between each PK parameter and the pertinent covariates

Parameter	CL (liters/h)	V_c (liter)	CL_D (liters/h)	V_t (liters)	$t_{1/2\beta}$ (h)
Wt (kg)	0.0544 (0.0076)[a]	0.187 (0.037)			
SAPS	−0.106 (0.019)	0.411 (0.096)	−0.218 (0.013)	0.397 (0.071)	0.272 (0.056)
CL_{CR} (ml/min)	0.0121 (0.0022)				−0.0405 (0.0063)
Intercept	0.201	−2.855	5.65	4.01	6.50

[a] Values in parentheses are SDs.

of isepamicin, which is solely eliminated by the kidneys, was expected to be decreased in ICU patients and highly variable among them. However, much of the interindividual variability of isepamicin PK parameters remained unexplained. It should be noted that CL_{CR} explained only 11% of the variability in isepamicin CL (while the inverse of the serum creatinine level was not a significant covariate), as was also reported by Fuhs et al. (4), who found a coefficient of correlation of only 0.36 between aminoglycoside and CL_{CR}. This low correlation is in contrast to that in studies on chronic renal failure, in which high correlations ($r = 0.937$) were found between CL_{CR} and isepamicin CL (8, 23), but ICU patients constitute a different and highly heterogeneous population.

Owing to these marked changes in isepamicin PK parameters, the question arises as to whether the dosing schedule should be modified in ICU patients. The simulated peak and trough concentrations of isepamicin in both populations (Table 6) showed that the mean trough concentration, which depends mainly on $t_{1/2}$, was higher in ICU patients, but not so high as to be of great concern. The median peak concentrations were similar in both populations, because the variations in V_c in the central compartment and CL compensate each other and resulted in only an 18% decrease in the first peak concentration of isepamicin in ICU patients. However, looking at the range of the peak concentrations in ICU patients revealed that it is less than 28 mg/liter in some patients, i.e., only twice the MIC at which 90% of isolates are inhibited for some bacterial strains. This finding merits some concern, since it has been shown that a favorable clinical outcome is correlated with a high peak concentration/MIC ratio (19). Therefore, monitoring of the isepamicin concentration is essential in ICU patients, and the use of a loading dose might be advisable. The determination of the best regimen in this population is under study.

TABLE 6. Simulation of isepamicin concentrations in the two populations after a 0.5-h infusion of 15 mg/kg once daily for 3 days

Group	Time (h)	Mean concn (mg/liter)	SD concn (mg/liter)	Median concn (mg/liter)	Perc1 (mg/liter)[a]	Per99 (mg/liter)[b]
ICU patients	0.75	55.5	14.5	53.6	28.7	95.4
	1	50.1	11.6	48.7	27.6	80.8
	24	2.7	2.6	2.0	0.1	12.2
	48.75	58.7	14.8	56.3	33.0	100.2
	72	3.5	4.5	2.2	0.1	19.0
Healthy volunteers	0.75	67.4	15.1	65.7	36.7	109.6
	1	57.1	10.9	56.1	34.7	83.6
	24	0.1	0.2	0.0	0.0	1.05
	48.75	67.5	15.0	37.1	37.1	109.6
	72	0.1	0.2	0.0	0.0	1.1

[a] Perc1, first percentile of the concentration distribution.
[b] Per99, 99th percentile of the concentration distribution.

APPENDIX

Principle of P-PHARM. P-PHARM software is based on an EM-like algorithm for estimating the population parameters of a nonlinear mixed-effect model given sparse individual data (18). This algorithm is a special kind of iterative two-stage method in which both random and fixed effects are included in the model. Each iteration is composed of two steps. At iteration k, the E step (expectation step) consists of estimating the PK parameters of each individual by the Bayesian MAP estimator, given the current estimate of the population parameters. The M step (maximization step) consists of estimating the population PK parameters by maximum likelihood, given the current estimate of the individual parameters and using a first-order expansion of the model about the individual parameters. These two steps are repeated until convergence, i.e., when the relative change between two iterations for each of the population parameters is less than 1%. The choice of the parameterization of the model is free. The distribution of each PK parameter can be assumed to be normal or log-normal, and all of the PK parameters do not need to follow the same form. However, covariances are always assumed to be zero; i.e., the covariance matrix is diagonal. Residual error is assumed to be additive to the concentration, with zero mean and variance either constant or proportional to the concentration or to the squared concentration. In the latter case, the proportionality coefficient is estimated as a population parameter by the EM algorithm.

Building the population model proceeds in three steps. First, the population PK parameters are estimated, with the covariates being ignored. Second, a linear covariate model is determined by multiple linear regression analysis between the Bayesian MAP estimates of the individual PK parameters and all of the available covariates. Third, the population PK parameters are estimated again, taking into account the covariates. Specifically, the individual parameters in the E step are obtained by the MAP estimator given the covariates of each individual.

Principle of POPSIM. POPSIM is software written in Visual Basic, version 3.0, which is devoted to the simulation of concentration kinetics in population models. The user must specify the structural PK model relating the concentration to dose, PK parameters, and time in an individual; the distribution (normal or log-normal) of each PK parameter in the population and its characteristics (mean vector and covariance matrix); the covariates model, i.e., the relationships between PK parameters and the covariates; the distribution (uniform, normal, or log-normal) of each covariate in the population and its characteristics; the dosing schedule and the times at which concentrations must be calculated; and the number of sample vectors (subjects) in the simulation.

These pieces of information are written in specific subroutines, which provide complete flexibility in the simulations. The algorithm proceeds as follows: A random vector of covariates is generated according to the specified distribution. The corresponding adjusted population PK parameter values are calculated according to the covariates model. A random vector of individual PK parameters is generated according to the adjusted distribution. The concentrations at desired sampling times, given the dosing schedule and the PK model, are simulated. Finally, the simulated concentrations are stored for descriptive statistics.

The generation of random deviates is based on a multiplicative congruent algorithm (subroutines ran 1 and gasdev) (22), after suitable

transformation in the case of a log-normal distribution (3). Simulation of the concentrations follows the principle of superposition in the case of repeated dosing. Descriptive statistics include mean, SD, percentiles (subroutine sort) (22), and histogram.

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