Analyzing Rich Data Using Different Methods Provided by NONMEM: Pharmacokinetics of Telmisartan Following Intravenous Infusion to Healthy Volunteers

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INTRODUCTION

Although NONMEM (nonlinear mixed effects modeling) has been proposed as a modeling tool for rich data sets, little work has described its application to evaluate pharmacokinetic data from Phase I studies (1). Telmisartan is a novel, nonpeptide angiotensin II receptor antagonist, which is orally active as an antihypertensive. To analyze sparse data of population kinetic studies in progress, it is necessary to have preliminary knowledge on the pharmacokinetic model describing the pharmacokinetic behavior of telmisartan. For this purpose mean population pharmacokinetic parameters of telmisartan following an intravenous infusion were assessed, and interindividual and residual variabilities were characterized. In addition, individual estimates of the structural pharmacokinetic parameters were computed. The data used for this investigation originate from a study where the absolute and relative bioavailability of 40 mg telmisartan administered to 12 healthy male volunteers were determined (2). This presentation focuses on data analysis and illustrates the use of different NONMEM methods with plentiful data.

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ABBREVIATIONS: Cl [l/h], Total body clearance; %CV [%], Percent coefficient of variation; FO, First-order estimation method; FOCE, First-order conditional estimation method; k_{ij} [1/h], Transfer rate constant (first-order) from compartment i to compartment j; %RSE [%], Percent relative standard error of estimate; SD, Standard deviation; SE, Standard error; V_c [l], Apparent volume of central compartment; θ, structural kinetic parameter; η, Random variable describing interindividualvariability; ω^2, Variance of η; ε_1, ε_2, Random variables describing residual variability; σ_1^2, σ^2, variances of ε_1, ε_2.

METHODS

Data

This study was conducted as a 3-way crossover, randomized, open trial. Only those concentration-time profiles obtained following intravenous infusion were included in this data analysis, particularly to gain knowledge on the parameters volume of distribution and total body clearance. Plasma levels of telmisartan were collected at the following time points: before administration and 0.0833, 0.125, 0.167, 0.25, 0.333, 0.417, 0.483, 0.517, 0.55, 0.6, 0.65, 0.75, 1.0, 1.25, 1.5, 2.5, 3.5, 6.5, 8.5, 12.5, 24.5, 48.5, and 72.5 hours after the start of the infusion. This trial was conducted according to the principles of the Declaration of Helsinki in its actual versions, the guidelines of the WHO and in accordance with the German Drug Act (AMG). Volunteers provided written consent before enrollment in the study.

Data Analysis

The measured concentration-time profiles of telmisartan were analyzed using the NONMEM program (double precision, version IV, level 2.1) running on a Pentium Pro PC under the DOS operating system (3). Preliminary analyses of the concentration-time profiles using two-, three-, and four-compartment models indicated that the three-compartment model was most appropriate. From theory it is well known that the eigenvalues of mammillary compartment models are always real (4), and therefore the three-compartment model was realized using the PREDPP subroutine ADVAN7. The pharmacokinetic model was parameterized using the first order rate constants k_{21}, k_{31}, k_{10}, k_{12}, k_{13}, and the apparent volume of distribution of the central compartment V_c. Interindividual variability in the pharmacokinetic parameters was modeled using an exponential error model; for clarity, additional subscripts necessary to denote transfer between compartments have been omitted:

$$k_i = \hat{k} \cdot \exp(\eta_i^k),\ \eta_i^k \text{ i.i.d. } N(0,\omega_k^2) \qquad (1)$$

in which k_i is the value for k of subject i, $\hat{k}$ is the population mean value for k, and η_i^k are independent, identically distributed random variables with zero mean and variance equal to ω_k^2 that distinguishes the i^{th} individuals parameter from the population mean as predicted by the regression model. This definition applies to all of the transfer rates in analogue form.

$$V_{c_i} = \hat{V} \cdot \exp(\eta_i^{V_c}),\ \eta_i^{V_c} \text{ i.i.d. } N(0,\omega_{V_c}^2) \qquad (2)$$

The interpretation of the model for interindividual variability in apparent volume of distribution of the central compartment is analogous to that of the rate constant. The correlations between η's were assumed equal to zero in the analysis reported here.

This model for interindividual variability assumes that the pharmacokinetic parameters are log-normally distributed, and the estimates are presented as percent coefficients of variation.

Residual variability represents the discrepancy in observed telmisartan concentrations and those predicted by the structural model in combination with the interindividual random effects model; it encompasses pharmacokinetic model misspecification, variability in the analytical method, deviations from trial protocol, and intraindividual variability. Preliminary analyses of the pattern of residuals and the reduction in standard error of the parameter estimates indicated that the residual variability

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was best described using a combined additive and proportional error model as shown in Equation 3:

$$C_{p_{ij}} = \hat{C}_{p_{ij}} \cdot (1 + \varepsilon_{1_{ij}}) + \varepsilon_{2_{ij}},$$
$$\varepsilon_{1_{ij}} \text{ i.i.d. } N(0,\sigma_1^2), \quad \varepsilon_{2_{ij}} \text{ i.i.d. } N(0, \sigma_2^2) \qquad (3)$$

in which $\hat{C}_{p_{ij}}$ is the j^{th} plasma concentration of subject i predicted using the pharmacokinetic model and regression equations for the typical values of the pharmacokinetic parameters specified above; $C_{p_{ij}}$ is the measured value of the j^{th} observed plasma concentration of subject i, and $\varepsilon_{1_{ij}}$, $\varepsilon_{2_{ij}}$ are random variables which represent the discrepancy between the j^{th} observed plasma concentration of subject i from the plasma concentration predicted from the regression model specified above, the $\varepsilon_{1_{ij}}$, $\varepsilon_{2_{ij}}$ are independent, identically distributed statistical errors with zero means and variances σ_1^2 and σ_2^2, respectively.

This model for residual variability assumes two types of ε's, ε_1 and ε_2, having possibly different variances. If the prediction is near zero, the variance is approximately constant, namely σ_2^2 (additive error model), whereas in case of being considerably greater than zero, the variance is approximately proportional to the squared prediction (constant coefficient of variation or proportional error model). Estimates of variance components ω^2's and σ_1^2 from NONMEM were converted into standard deviations by taking their square root. These are reported as coefficients of variation (%CV) after multiplying them by 100%. The estimate of the variance component σ_2^2 was converted into the standard deviation by taking the square root (SD). SD intervals of residual variability, as well as of interindividual plus residual variability of predicted concentrations were computed by NONMEM.

The goodness-of-fit of each NONMEM analysis was assessed by the examination of scatterplots of predicted versus measured plasma concentrations and weighted residual plots, the percent relative standard error (%RSE) of the mean of parameter estimates, and changes in the estimates of interindividual and residual variability.

No attempt was made to investigate the influence of covariates, since the studied population was rather homogenous with regard to the demographic data.

NONMEM Methods

The population mean parameters and variabilities were estimated using the methods FO (first-order estimation method), FOCE (first-order conditional estimation method) with and without the option INTERACTION. The approximate confidence intervals of predicted mean concentrations were calculated from the respective variances provided by NONMEM, applying linearisation with respect to random error terms using a first-term Taylor series approximation (5).

Five methods, referred to as methods 1, 2, 3, 4, and 5, were applied to obtain individual parameter estimates, these are described below:

Method 1 is a traditional single-subject analysis.

Method 2 uses the first-order estimation method (FO) and the POSTHOC option to obtain individual parameter estimates. These estimates are Bayesian estimates, based not only on the individual's data, but, importantly, also on values for the population parameters. They were obtained after the population parameter estimates had themselves been estimated. The so-called POSTHOC estimates are computed by NONMEM under the assumption that the variance model for each subject is that of the mean individual.

Method 3 is a modification of method 2. Two new variables were defined to account for individual variabilities according to

$$EX_1 = EXP(\eta_7) \cdot \sqrt{\theta_7} \text{ and } EX_2 = EXP(\eta_8) \cdot \sqrt{\theta_8}.$$

θ_7 and θ_8 were set equal to the typical values of σ_1^2 and σ_2^2 from the population run obtained from method 2. All the other structural θ's were frozen to the estimates resulting from method 2. EX_1 and EX_2 provide estimates of the individual σ's. All the ω^2's are set equal to very large values (=100), that the estimates are unconstrained by the priors. The σ^2's were set equal to 1, so that they do not influence the estimates. The estimation step included the method FOCE, the option INTERACTION and the maximum number of function evaluations was set equal to zero (cf. Appendix). This results in a modified single-subject analysis.

Method 4 uses FOCE without the option INTERACTION, whereas *method 5* uses FOCE with INTERACTION.

Methods 1 and 3 are characterized by the fact that they only comprise subject specific information to estimate the parameters of that specific subject. In contrast, methods 2, 4, and 5 take into account information both, certain information of all subjects and subject specific information.

RESULTS AND DISCUSSION

There was clear-cut evidence that modeling the data with a three-compartment model was most appropriate. A two-compartment and a four-compartment model were excluded by visual inspection of diagnostic plots.

Population Means and Variabilities

The methods FO and FOCE provide almost identical results with regard to both, population mean parameter estimates and variabilities. Goodness-of-fit scatterplots (observations versus predictions) reveal that FOCE along with the option INTERACTION performs slightly better than the above-mentioned methods. Parameter estimates do not differ much except for the estimates of k_{31} and σ_2: 0.085 l/h for FO, 0.078 l/h for FOCE and 0.056 l/h for FOCE with INTERACTION; 0.968 ng/ml for FO, 0.878 ng/ml for FOCE and 0.394 ng/ml for FOCE with INTERACTION, respectively. The population pharmacokinetic parameters obtained using FOCE and INTERACTION are summarized in Table I. The magnitudes of the standard errors of the parameter estimates were in the range of 7.4% (k_{10}) to 19.4% (k_{13}). An exponential model best described the interindividual variability for the pharmacokinetic parameters, the estimates of which (reported as %CV) were between 21.5% (V_c) and 57.1% (k_{13}). The corresponding percent relative standard errors were estimated as 36.2% (k_{13}) and 53.1% (k_{21}). The precision of the fixed effect parameters is considerably greater than that of the random effects parameter estimates, probably because the number of subjects available for this analysis is small. Individual plasma levels of telmisartan, the

Table I. Final Parameter Estimates and Variabilities Obtained with NONMEM Using FOCE and the Option INTERACTION (Method 5) from the Three-Compartment Model for Telmisartan

Parameter	Final estimate	Precision %RSE[b]	Final estimate %CV[a]	Precision %RSE[b]
k_{21} [1/h]	1.18	10.5	29.1	53.1
k_{31} [1/h]	0.0556	15.4	44.3	43.8
k_{10} [1/h]	2.93	7.43	24.3	51.8
k_{12} [1/h]	3.02	17.7	51.2	44.7
k_{13} [1/h]	1.19	19.4	57.1	36.2
V_c [l]	19.6	7.81	21.5	42.7
Residual variability				
σ_1	12.8 %CV[a]	17.4		
σ_2	0.394 SD[c]	117		

Note: Minimum value of objective function = 1781.
[a] Estimates of variance components (ω^2's and σ^2's) were converted into standard deviations by taking their square root. These are reported as coefficients of variation (%CV) after multiplying them by 100%.
[b] The percent standard error of parameter estimates was calculated according to %RSE = 100% standard error (SE)/ parameter estimate.
[c] The standard deviation was calculated as the square root of the variance ([ng/ml]).

population mean concentration-time profile and 1 SD intervals of residual variability and 1 SD intervals of interindividual plus residual variability are depicted in Fig. 1.

Individual Parameter Estimates

The single-subject analysis (method 1) provides identical results compared with method 3. Individual data analyses can be performed very expeditiously using method 3. All methods applied

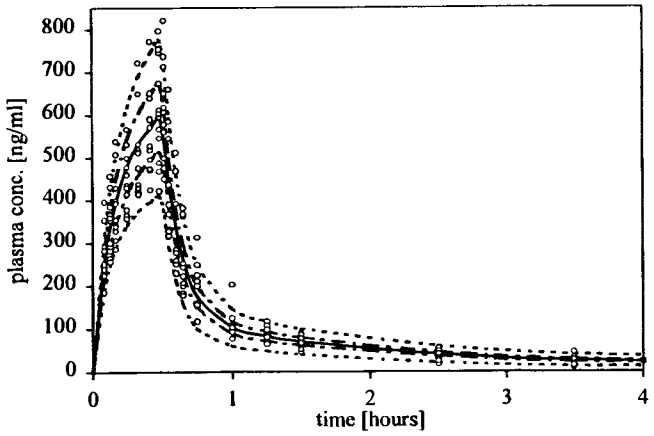

Fig. 1. Measured plasma concentration-time profiles of telmisartan in 12 healthy subjects following intravenous infusion of 40 mg telmisartan. The solid line is the concentration-time profile predicted in the typical individual using FOCE and INTERACTION (method 5). The area bounded by the broken lines (— –) represents the uncertainty in the predicted levels caused by residual variability (±1 SD). The area bounded by the outer broken lines (···) represents the uncertainty in the predicted concentrations produced by the sum of interindividual and residual variability (±1 SD); that is, about 68% of all telmisartan concentrations in a population of 'standard' individuals, might be expected to fall in this larger area.

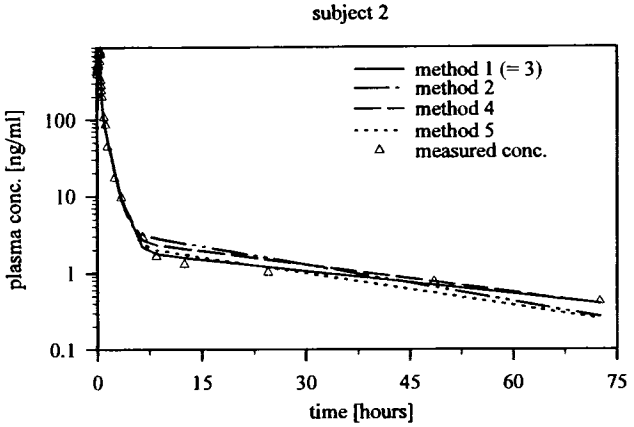

Fig. 2. Measured and individual plasma concentration-time profiles of telmisartan in subject 2 predicted from the individual parameters obtained with the different methods.

to evaluate the data provide similar results. Inspection of the graphs reveals minor discrepancies in 9 of 12 volunteers. Differences can only be detected within the terminal phase of the plasma concentration-time profiles (24.5 to 72.5 hours) in subjects 2, 4, 5, 6, 7, 8, 9, 11, and 12; as well as within the interval 6.5 to 12.5 hours in subjects 2, 9, and 12. Individual plasma levels of telmisartan and individual predicted concentration-time profiles of subjects 2, 5, 7, and 8 showing typical differences between the compared methods are illustrated in Figs. 2 to 4.

Surprisingly, method 1 (=3) does not perform well with subjects 4, 5, 7, and 11 (Figs. 3 and 4), whereas method 4 does not characterize well the concentration-time profiles of subjects 2, 4, 7, 8, and 12 (Figs. 2 and 4).

Method 2 shows deficiencies to fit the data of subjects 2, 4, 7, 8, 9, and 12 (Figs. 2 and 4). This is likely related to the fact that i) the Bayesian estimates are influenced by the prior information associated with residual variability and ii) the prior information concerning interindividual variability results in shrunken estimates toward the prior means.

Predominantly, method 5 was found superior to the other methods and even surpasses the single-subject analysis with respect to subjects 4, 5, 7, 11, 12 (Figs. 3 and 4). The strengths of method

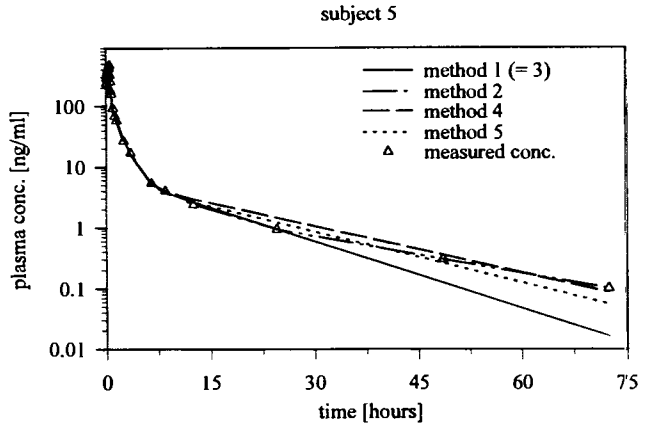

Fig. 3. Measured and individual plasma concentration-time profiles of telmisartan in subject 5 predicted from the individual parameters obtained with the different methods.

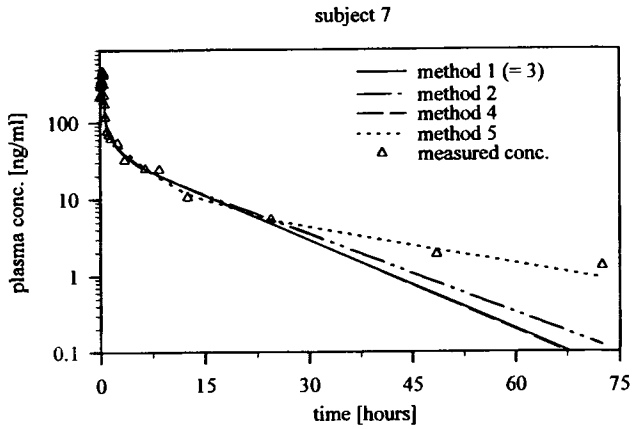

Fig. 4. Measured and individual plasma concentration-time profiles of telmisartan in subject 7 predicted from the individual parameters obtained with the different methods.

5 compared with the single-subject analysis is that it takes into account information from all individuals collectively, as well as information about the individual's measurement data. The individual parameter estimates resulting from this method are presented in Table II. Percent deviations of individual parameters of methods 1 (= 3), 2 and 4 in relation to method 5 are given in Table III. They consistently reveal certain differences between the applied methods.

CONCLUSIONS

Extensive concentration-time profiles deliver valuable information on the pharmacokinetics of new compounds, which is particularly important for planning and analyzing large Phase III/IV population pharmacokinetic studies. NONMEM offers powerful methods and great flexibility to handle error models to perform such data analyses. Apart from individual fits the total population is characterized. Overall, the performance of all methods with regard to population mean estimates and variabilities is very similar. Individually, the data appear to be best characterized using method 5, the first-order conditional estimation method (FOCE) taking interaction into account. The results of this investigation suggest this method performs best with plentiful data. It turned out that method 3 is a quick and numerically stable procedure to perform single-subject analyses.

APPENDIX

NONMEM code to implement method 3:

```
PROBLEM TELMISARTAN
$INPUT ID TIME AMT RATE CP = DV EVID MDV
$DATA DPIV1.DAT RECORD = 284
$SUBROUTINES ADVAN7, TRANS1
$MODEL COMP(CENTRAL,NOOFF,DEFOBS,DEFDOSE)
    COMP(PERIF2,NOOFF)
    COMP(PERIF3,NOOFF)
$PK
    TK21 = THETA(1) TYPICAL VALUES
    TK31 = THETA(2)
    TK10 = THETA(3)
    TK12 = THETA(4)
    TK13 = THETA(5)
    TVS1 = THETA(6) ;S1 = SCALING OF CENTRAL CPT
    K21 = TK21*EXP(ETA(1))
    K31 = TK31*EXP(ETA(2))
    K10 = TK10*EXP(ETA(3))
    K12 = TK12*EXP(ETA(4))
    K13 = TK13*EXP(ETA(5))
    S1 = TVS1*EXP(ETA(6))
    EX1 = EXP(ETA(7))*DSQRT(THETA(7))
    EX2 = EXP(ETA(8))*DSQRT(THETA(8))
$ERROR
    IPRED = F
    IRES = CP-IPRED
    DEL = 0
    IF (IPRED.EQ.0) DEL = 1
    IWRES = (1-DEL)*IRES/(IPRED + DEL)
    Y = F*(1 + EX1*ERR(1)) + EX2*ERR(2)
$THETA 1.2439 0.084869 2.8943 2.8228 1.6283 19.658
$THETA 0.0174
$THETA 0.937
$OMEGA 100. 100. 100. 100. 100. 100. 100. 100.
$SIGMA 1.
$SIGMA 1.
```

Table II. Final Individual Bayesian Parameter Estimates Obtained with NONMEM Using FOCE and the Option INTERACTION (Method 5) from the Three-Compartment Model for Telmisartan

Parameter	k_{21} [1/h]	k_{31} [1/h]	k_{10} [1/h]	k_{12} [1/h]	k_{13} [1/h]	V_c [l]	Cl[a] [l/h]
Subject 1	1.077	0.0600	3.089	5.907	2.372	13.2	40.7
Subject 2	1.646	0.0375	5.119	2.784	0.856	14.4	73.5
Subject 3	1.610	0.0431	2.437	1.512	0.548	25.3	61.8
Subject 4	1.281	0.1170	2.549	2.851	2.171	18.9	48.1
Subject 5	1.372	0.0796	3.896	3.411	0.863	22.7	88.5
Subject 6	1.312	0.0303	2.563	4.654	2.044	18.5	47.4
Subject 7	0.620	0.0563	2.290	5.570	1.113	21.0	48.2
Subject 8	1.174	0.0717	2.613	2.276	1.012	22.7	59.4
Subject 9	1.307	0.0343	3.359	2.292	1.137	21.3	71.6
Subject 10	0.899	0.0557	2.512	4.535	2.352	15.7	39.4
Subject 11	1.437	0.0849	2.516	3.646	1.646	24.0	60.4
Subject 12	0.986	0.0487	3.343	1.134	0.441	21.0	70.4

[a] Clearance was calculated as the product of k_{10} and V_c.

Table III. Percent Deviations of Individual Parameter Estimates of Methods 1 (=3), 2, and 4 in Relation to Method 5

Subject	Method	k_{21} %	k_{31} %	k_{10} %	k_{12} %	k_{13} %	V_c %	Cl[a] %
1	1	−6.2	−0.9	−15.0	−18.4	−17.1	19.9	1.9
	2	−2.3	−7.0	−0.6	3.2	2.0	−0.1	−0.7
	4	−4.8	−7.3	−4.3	−2.2	−2.6	4.0	−0.4
2	1	1.9	38.0	−7.9	−18.3	−19.7	11.8	3.0
	2	−5.2	−16.4	−0.5	−7.2	−23.7	4.2	3.7
	4	−1.5	12.1	−2.4	−10.8	−25.9	7.5	5.0
3	1	17.9	3.0	10.7	43.7	14.2	−9.6	0.1
	2	−9.3	−18.6	1.6	2.9	−4.4	0.0	1.6
	4	2.5	−5.3	5.4	16.7	5.1	−4.0	1.2
4	1	−35.4	−28.7	−11.7	−7.9	−19.8	7.5	−5.1
	2	−9.5	−19.7	−5.3	1.8	−5.7	1.7	−3.7
	4	−12.6	−25.7	−7.4	3.5	−8.6	2.7	−5.0
5	1	−8.4	−23.3	−5.1	−6.1	0.6	3.9	−1.4
	2	−2.9	5.1	3.8	2.6	−17.5	0.7	4.5
	4	−1.2	6.4	2.1	1.3	−11.1	1.2	3.3
6	1	−1.4	16.2	0.9	−7.5	−5.8	3.9	4.8
	2	3.3	−15.2	−5.5	2.4	8.1	0.2	−5.3
	4	3.5	−5.0	−5.4	−1.6	4.9	2.2	−3.3
7	1	−36.8	−73.6	−11.1	57.4	−62.5	1.1	−10.1
	2	−36.8	−69.3	−9.4	45.5	−60.1	2.1	−7.5
	4	−49.2	−75.2	−13.2	67.6	−67.7	3.7	−10.0
8	1	15.0	13.0	7.0	10.8	9.1	−4.9	1.7
	2	−7.5	−10.5	−1.1	0.5	−3.5	1.0	−0.1
	4	−7.3	−13.0	−1.0	1.5	−0.2	0.1	−0.9
9	1	2.8	22.4	5.4	2.1	−8.2	−1.4	3.9
	2	−1.4	−29.2	−1.8	−0.4	2.1	−0.9	−2.7
	4	−0.1	−10.3	0.5	−1.3	−1.2	−0.9	−0.5
10	1	2.7	4.3	−2.1	−3.9	−2.8	4.7	2.5
	2	−2.3	−9.3	−2.0	1.5	0.0	0.8	−1.2
	4	−6.0	−9.6	−4.1	−2.9	−3.3	3.3	−0.8
11	1	−11.2	−18.4	−1.9	1.1	0.6	−1.7	−3.6
	2	−1.7	−9.5	−4.4	0.1	0.4	2.6	−1.8
	4	−1.0	−10.1	−3.7	1.2	1.4	1.8	−2.0
12	1	16.1	−3.8	3.6	18.3	23.9	−3.9	−0.4
	2	−14.4	−15.4	3.2	1.2	−29.3	1.5	4.7
	4	−13.9	−8.6	2.4	0.8	−20.6	0.9	3.3

[a] Clearance was calculated as the product of k_{10} and V_c.

```
$ESTIMATION METHOD = 1 INTERACTION PRINT = 5
  MAXEVAL = 0
NOABORT
$TABLE K21 K31 K10 K12 K13 S1 ETA1 ETA2 ETA3 ETA4
  ETA5 ETA6
EX1 EX2
    NOPRINT FILE = TEL1.ASC
$TABLE TK21 TK31 TK10 TK12 TK13 TVS1 NOPRINT
  FILE = TEL1.ASC
$TABLE ID TIME IPRED IRES IWRES NOPRINT FILE
  = TEL1.ASC
```

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