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ORIGINAL ARTICLE

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Effects of demographic variables on vorozole pharmacokinetics in healthy volunteers and in breast cancer patients

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Abstract *Purpose*: Vorozole (VOR) is a selective nonsteroidal inhibitor of the cytochrome P450-dependent aromatase that catalyzes the conversion of androgens to estrogens. It is currently being developed as a therapeutic agent in the endocrine treatment of postmenopausal women with breast cancer. This work was aimed to explore the effects of demographic and other variables on VOR pharmacokinetics. *Methods*: VOR plasma concentration-time data were obtained in healthy volunteers and in breast cancer patients after the oral administration of 2.5 mg of VOR as a single dose or once daily. The data obtained in 6 formal pharmacokinetics (PK) studies with frequent plasma sampling were included in the data base (84 healthy male and female volunteers and 13 breast cancer patients). Also included were data from 2 clinical efficacy trials involving 286 breast cancer patients who were treated for several months (1 sample per visit, up to 14 samples/patient). The nonlinear mixed-effect modeling (NONMEM) approach was applied. The two-compartment linear PK model with first-order absorption parameterized in terms of apparent clearance (CL), apparent central and peripheral volumes of distribution (Vc and Vp, respectively), apparent distributional flow (Q), and absorption constant (k_a) was used. A population model was developed using data from formal PK studies. The final estimates of fixed and random effect parameters were obtained using both formal study data and clinical-efficacy trial data. *Results*: The typical CL value obtained after a single dose was lower in patients (4.8 l/h) as compared with healthy volunteers (8.6 l/h) and did not depend on gender. The multiple- to single-dose ratio was 0.76. CL was constant over ages of up to 50 years and then decreased slightly (0.047 l/h per year). The typical CL value did not depend on any demographic variable related to body size (total body weight, WT; body surface area; lean body mass). Q and Vc were proportional to WT (0.17 l h^{-1} kg^{-1} and 0.43 l/kg, respectively). Vp was also proportional to WT and was higher in women as compared with men (0.64 and 0.40 l/kg, respectively). The same was true for the apparent steady-state volume of distribution. No effect of race or the duration of therapy (0.5–28 months) was seen. The unexplained variability in CL and the residual variability in VOR plasma concentrations were 39% and 28% (coefficient of variation), respectively. *Conclusions*: Healthy volunteer/patient, single/multiple dosing differences, and age were identified as the fixed effects influencing the CL of VOR. WT was the main determinant of distributional PK parameters. The peripheral and steady-state volumes of distribution were gender-dependent. In view of the relatively high degree of residual interpatient variability in CL, the slight effect of age on it is unlikely to be clinically significant.

Key words Vorozole · Population pharmacokinetics · NONMEM

Abbreviations *BSA* Body surface area · *CL* Apparent clearance · *CV* Coefficient of variation · *HT* Body height · k_a Absorption rate constant · *LBM* Lean body mass · *MOF* Minimal objective function · *Q* Distributional flow · *SD* Standard deviation · *SE* Standard error of estimate · $t_{1/2}$ Terminal half-life · *Vc* Central volume of distribution · *VOR* Vorozole · *Vp* Peripheral volume of distribution · *Vss* Steady-state volume of distribution · *Vz* Volume of distribution in the terminal phase · *WT* Body weight

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Introduction

Vorozole (VOR) is a selective nonsteroidal inhibitor of the cytochrome P450-dependent aromatase that catalyzes the conversion of androgens to estrogens [11, 12].

It is currently being developed as a therapeutic agent in the endocrine treatment of postmenopausal women with breast cancer [5]. VOR pharmacokinetics has been studied in healthy volunteers (both men and women) as well as in the target patient population. The aim of the present analysis was mainly to explore the effects of demographic variables and other factors that potentially influence VOR pharmacokinetic (PK) parameters.

The nonlinear mixed-effect modeling (NONMEM) method [1] was used throughout the work. Two kinds of VOR plasma concentration-time data were available: data obtained in formal PK studies (numerous samples per subject) and those from clinical efficacy trials (only one sample per visit). For each patient there were several visits that might have been separated by 2 weeks or more. As data from the efficacy trials were scarce, the VOR population PK model was completed using the formal-study data only. Then, clinical trial data were included in the data base and final estimates for the model parameters were obtained.

Subjects and methods

PK data included in the data base

The data subjected to NONMEM analysis were obtained from five formal PK studies in healthy volunteers (studies I–V), one formal PK study in breast cancer patients (study VI), and two clinical efficacy trials in breast cancer patients (studies VII and VIII). The number of subjects in each study and their demographic characteristics are summarized in Table 1. As can immediately be seen, the dosing and sampling protocols significantly differed from study to study. A total of 84 healthy volunteers (24 men and 60 women) and 13 breast cancer patients participated in the formal PK studies, in which a number of blood samples were obtained from each subject. In the clinical efficacy trials, VOR was given for several months, and up to 14 blood samples (one per visit) were available from each of the 286 breast cancer patients who were included in the present analysis.

VOR was given orally as a solution or tablets at a dose of 2.5 mg (as a single dose or once daily). As no statistically significant difference was found in either the extent of bioavailability or the absorption rate of VOR from the solution or tablets (unpublished results), the formulation was not considered as a covariate that might affect any PK parameter.

The concentration of VOR in plasma samples was measured using gas chromatography with electron-capture or thermoionic detection. The calibration curves were linear over concentrations ranging from 0.5 (quantification limit) to 200 ng/ml, and the mean between-day CV over the whole concentration range was ≤5%.

The following covariates were tested as potential determinants of the PK parameters of VOR: age (years), gender, body weight (WT, kg), body length (HT, m), body surface area (BSA, m^2; calculated according to Haycock et al. [4]), lean body mass (LBM, kg; calculated according to Morgan and Bray [8], study number, healthy volunteers/patients, single/multiple dose, country, race, and the duration of therapy (months). The latter three factors were tested only for studies VII and VIII.

Building and validation of a population PK model

The NONMEM program, version IV, level 1.3; NM-TRAN, version III, level 1.1; and PREDPP, version II, level 1.3 were used throughout the analysis. The software was running on a HP-9000 workstation operating under HP/UX. The first-order conditional estimation (FOCE) method with interaction was used for fitting of models to the data.

The population PK model was built in several steps. First, a preliminary model containing no covariate was fitted to the data from the formal PK studies only. The interindividual variability in each structural parameter, P, was modeled as follows: $P_j = \hat{P}\exp(\eta_{P,j})$, where P_j is a "true" individual parameter value in the jth subject, $\hat{P}$ is a typical value in the population, and $\eta_{P,j}$ is a random variable with zero mean and variance $\omega_P{}^2$. As the correlation between η values was neglected, the interindividual variance-covariance matrix was assumed to be diagonal.

The residual variability in VOR plasma concentration was initially modeled as a sum of proportional and additive terms: $C_{ij} = \hat{C}_{ij}\exp(\varepsilon_{ij,1}) + \varepsilon_{ij,2}$, where C_{ij} and $\hat{C}_{ij}$ are the ith measured and the model-predicted VOR concentrations in the jth subject, respectively, and $\varepsilon_{ij,1}$ and $\varepsilon_{ij,2}$ denote the residual intrasubject errors distributed with zero means and variances σ_1^2 and σ_2^2, respectively.

After fitting of the preliminary model to the formal study data, conditional (Bayesian) estimates of individual PK parameters produced by the NONMEM program were plotted versus the covariates. The "full" population model was then constructed by making $\hat{P}$ a function of those covariates that displayed an evident impact on PK parameters and produced a decrease in the minimum of the objective function (MOF) by 4 units or more ($P < 0.05$). The fixed-effect parameters were then eliminated from the model one at a time, and if MOF did not increase by more than 6.6 ($P < 0.01$) and the standard error of parameter estimate exceeded 50%, the corresponding parameter was finally excluded from the model.

The adequacy of the final model was checked by the analysis of residuals and by the visual inspection of plots of predicted versus measured concentrations. The predictive performance was assessed by (a) graphical analysis of the VOR plasma concentration predictions recorded for the patients of studies VII and VIII versus the levels actually measured, (b) the mean prediction error (the prediction error equals the population prediction, i.e., including fixed effects, minus the measured value [10]) as the measure of prediction bias, (c) the ratio of a prediction-error standard deviation to a predicted value as the measure of prediction precision, and (d) the visual examination of plots of weighted residuals versus covariates for these studies.

In the last step the final estimates of parameters were obtained by fitting of the model to the combined data set containing all available data. Individual Bayesian estimates of structural model parameters for further statistical and graphical analysis were generated by the NONMEM program. Two additional parameters were also calculated: the steady-state volume of distribution (Vss) and the terminal half-life ($t_{1/2}$) [2].

In studies VII and VIII, many patients were sampled more than once during the treatment. This allowed us to assess, at least approximately, the magnitude of interoccasion (between visits) variability. For this purpose a set of visit-specific estimates of η values (as coming from different individuals) were produced for each patient and deviations from the normal individual η value (i.e., pooling of all visits for this patient together) were calculated. These deviations for all subjects were pooled, and the corresponding SD was regarded as the approximate interoccasion CV for a particular PK parameter.

Statistical analysis

S-PLUS software [8] was used for the graphical and statistical analysis.

Results

Structural model

Figures 1 and 2 give examples of the typical formal PK-study data and the clinical-efficacy trial data,

Table 1 Description of the data included in the NONMEM analysis of vorozole pharmacokinetics

Study	Number of subjects, males (*M*) or females (*F*), race (*C* Caucasian, *NC* other race)	Median age (min–max)	Median WT (min–max)	Median HT (min–max)	Number of samples per subject	Time of the last sample (h)	Details
I	6 M, C	38.5 (32–47)	75 (68–90)	178 (166–184)	7	24	Healthy volunteers, 2.5-mg single dose
II	6 M, C	33.25 (27–36)	77 (64.5–102)	183.5 (170–190)	43	364	Healthy volunteers, 2.5 mg once daily for 14 days
III	12 F, C	59 (53–64)	67 (55–83)	163 (157–175)	25	216	Healthy volunteers, 2.5 mg once daily for 8 days except for day 2, when the dose was omitted
IV	24 F, C	56 (48–64)	69.5 (53–89)	165 (153–178)	12	48	Healthy volunteers, 2.5-mg single dose
V	12 M, C	21 (18–26)	69 (60–85)	183 (171–190)	11	56	Healthy volunteers, 2.5-mg single dose
	12 F, C	55 (50–65)	67 (60–82)	168 (159–178)	*Idem*	*Idem*	*Idem*
	12 F, C	73 (70–84)	69 (50–83)	161 (154–170)	*Idem*	*Idem*	*Idem*
VI	13 F, C	53 (40–78)	67 (52–75)	165 (154–169)	24	216	Postmenopausal breast cancer patients, 2.5 mg once daily for 8 days except for day 2, when the dose was omitted
VII	199 F, 22 NC	66 (37–93)	68 (42–100)	162 (145–184)	1–4[a]	0–144	Postmenopausal breast cancer patients, 2.5 mg once daily for several months
VIII	87 F, 4 NC	67 (45–84)	70 (28.5–111)	159 (132–174)	*Idem*	*Idem*	*Idem*

[a] One sample per visit; 1- to 2-month interval between visits

respectively (open circles). Since the postpeak parts of the plasma concentration-time curves generated in all formal studies (like that shown in Fig. 1) were apparently biexponential, the two-compartment model with first-order absorption was selected. The one-compartment model with first-order absorption was selected. The one-compartment model would not have been adequate and the three-compartment model would obviously have been too complex to be fitted to the data. The dispositional part of the selected model was parameterized in terms of clearance (CL), volumes of compartments (Vc and Vp for the central and peripheral compartments, respectively), and distributional flow (Q). No absorption lag time was included since the lack of plasma samples early after dosing did not allow its proper estimation. Thus, together with the absorption rate constant, k_a, there were five structural parameters in the model. Since VOR was given orally, all parameters related to its distribution and elimination were relative to the (unknown) systemically available dose fraction.

Building of the population model

The population model for the determination of VOR PK was completed using only data from the formal PK studies (studies I–VI, Table 1) obtained in 97 subjects (breast cancer patients as well as healthy volunteers of both genders). After graphical analysis of the individual Bayesian estimates of CL, Vc, Vp, Q, and k_a that were obtained by fitting of the preliminary model, the following covariates were identified as potential fixed effects (in parentheses the affected PK parameters are specified): age (CL); WT, BSA, and LBM (CL, Vc, Vp, and Q); sex (CL and Vp); healthy volunteers/patients (CL); single/multiple dosing (CL and k_a); and study number (studies III and VI were associated with lower CL).

When plotted versus age, CL was almost unchanged between 20 and 50 years and then decreased. Thus, a regression model in the form of a piecewise linear function was assumed in this case. The specific effects of

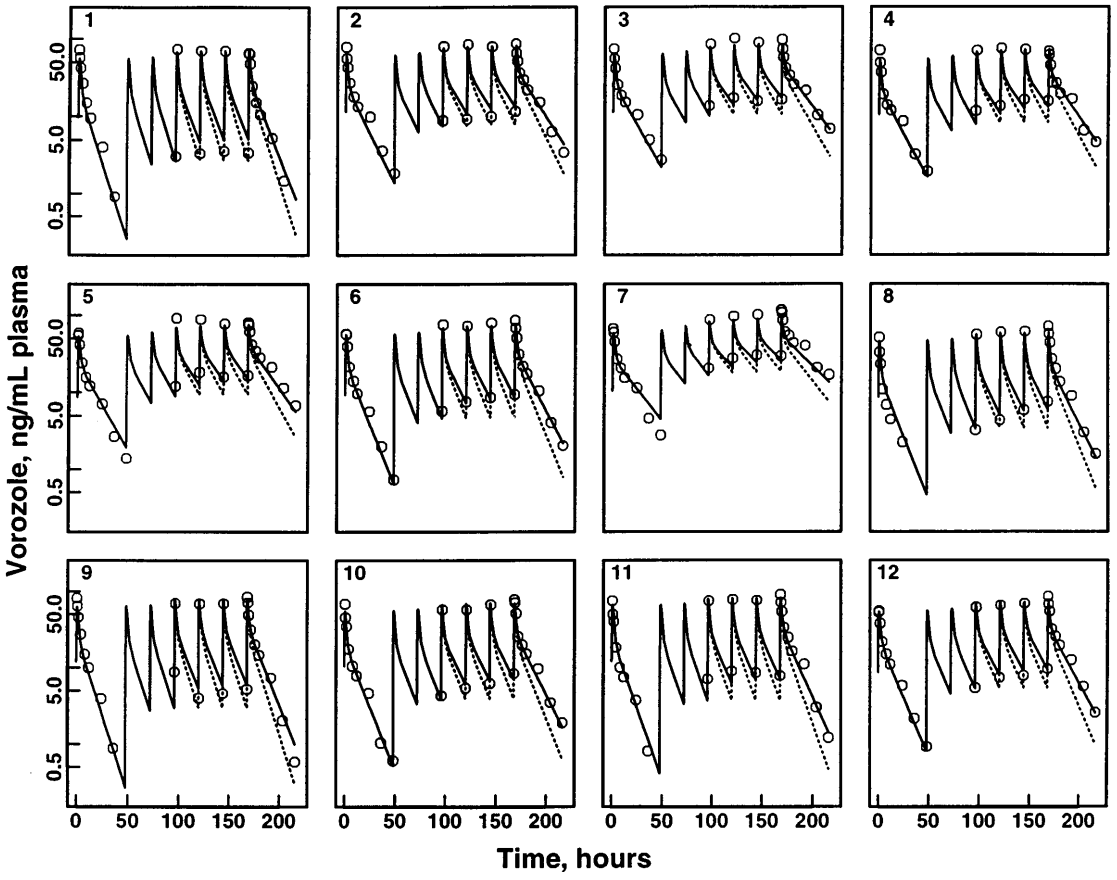

Fig. 1 Example of individual VOR plasma concentration-time measurements (*circles*) in healthy volunteers (study III) dosed with 2.5 mg/day for 8 days (the second dose was skipped). The *lines* are model predictions based on the Bayesian estimates of VOR PK parameters. The *continuous lines* correspond to the final model that includes the single/multiple dose difference in clearance, whereas the *dotted lines* are predictions based on the clearance value obtained after a single dose

gender and of any of the body size variables on CL became insignificant after the inclusion of age, healthy volunteer/patient difference, and study difference as fixed effects. The difference in CL observed between study VI and the other studies was completely explained by the healthy volunteer/patient difference. However, VOR clearance remained significantly lower in study III after the incorporation of all fixed effects in the regression model for CL. The final model for the typical CL value is as follows:

$$\hat{\mathrm{CL}} = [(1-\mathrm{PAT})\times\theta_1 + \mathrm{PAT}\times\theta_2][1-\mathrm{MLT}\times(1+\theta_3)] \times [1-\mathrm{STU}\times(1+\theta_4)] + \mathrm{AG}_{50}\theta_5(50-\mathrm{AGE}) \ .$$

The indicator variable *PAT* equals 0 for healthy volunteers and 1 for patients. Thus, θ_1 and θ_2 correspond to basal (not affected by age) clearance values in healthy volunteers and patients, respectively, after single-dose administration. *MLT* equals 0 and 1 in the case of single and multiple administration, respectively, and θ_3 reflects

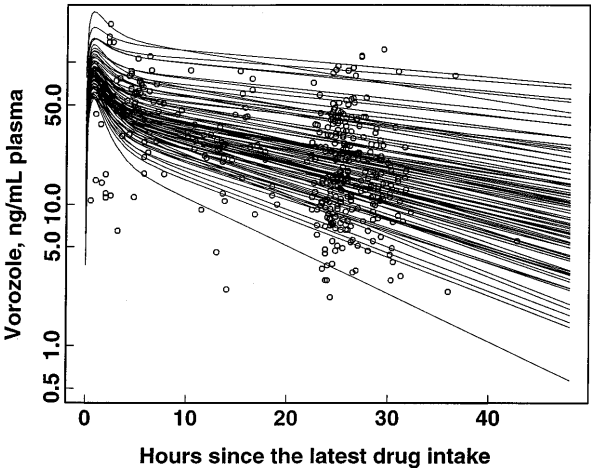

Fig. 2 Example of individual VOR plasma concentration-time measurements (*circles*) in breast cancer patients (study VIII) who received 2.5 mg/day. The *lines* are model predictions based on the Bayesian estimates of VOR PK parameters

the reduction in CL at multiple dosing. The indicator variable *STU* equals 1 in the case of study III and zero otherwise; thus, θ_4 is the relative CL value obtained in subjects of study III as compared with the other studies. Finally, the indicator variable AG_{50} equals 1 for subjects older than 50 years and zero otherwise, and θ_5 is the rate of decrease in CL with age after 50 years.

The single/multiple dose difference in CL is illustrated by the predicted (Bayesian) individual plasma concentration-time curves of study III plotted in Fig. 1 together with the measured VOR levels. The dotted lines correspond to the profiles simulated under the assumption that CL found after single-dose administration does not change at multiple dosing, whereas the continuous lines represent the profiles predicted by the final model, which incorporates the single/multiple dose difference.

As covariates reflecting the body size were highly correlated and it was not possible to find any preference for one covariate over others, WT was selected as the only body size variable affecting Vc, Vp, and Q. It was first included in the model in the form of linear equations with nonzero intercepts; however, after model fitting, all of the latter were found to be negligible and were excluded from the final model, which was as follows:

$$\hat{V}_c = WT \times \theta_6$$

$$\hat{V}_p = (1 - SEX) \times WT \times \theta_7 + SEX \times WT \times \theta_8$$

$$\hat{Q} = WT \times \theta_9 \ .$$

Thus, all distributional parameters were proportional to WT. Besides this, Vp was found to be strongly dependent upon gender (the indicator variable *SEX* was 0 for male and 1 for female), and θ_7 and θ_8 corresponded to male and female, respectively.

The absorption rate constant was found to be different after single and multiple dosing: $k_a = (1 - MLT) \times \theta_{10} + MLT \times \theta_{11}$, where θ_{10} and θ_{11} are the absorption rate constant after single-dose administration and at multiple dosing, respectively.

After the inclusion of all significant fixed effects into the model, the additive term of the residual error model vanished and the single variance σ^2 related to the proportional error was the only parameter reflecting the unexplained intraindividual variability observed in VOR plasma concentration.

The final model was fitted to the formal study data to get estimates of all θ values as well as of ω values associated with the unexplained interindividual variability seen in structural PK parameters. The interindividual variability in Q turned out to be negligible, and the corresponding ω was excluded. After plotting of population predictions versus measured VOR plasma levels, no significant bias could be seen. There was also no trend in the plots of weighted residuals (produced by the NONMEM program) against covariates; thus, the model describes the fixed effects of available covariates well. No correlation between any pair of model parameters was seen. In the correlation matrix generated by NONMEM, all elements were less than 0.64 (not shown).

The mean error of population predictions of VOR plasma concentrations for the patients of studies VII and VIII (0.023 ng/ml) did not differ significantly from zero (95% confidence interval −0.027 to 0.074 ng/ml; $P = 0.363$), indicating no bias in the model predictions. Also, there was no bias in the population predictions plotted against measured plasma concentrations for these studies. The prediction precision was 73%.

Since the data from the clinical efficacy trials (studies VII and VIII) were sparse and few samples were taken shortly after the dose intake, they would hardly provide any information about VOR absorption kinetics. Therefore, before fitting of the model to the combined data set containing the data from all studies, θ_{10} and θ_{11} as well as ω reflecting the interindividual variability in k_a were fixed at the corresponding estimates obtained in the formal PK studies.

Bayesian estimates of CL for the patients of studies VII and VIII were analyzed graphically against additional covariates available in these studies. No effect of the duration of therapy (up to several months), the race, or the participating country was seen.

Final parameter estimates

The final estimates of VOR population model parameters, together with their standard errors, are displayed in Table 2. Continuous lines plotted in Figs. 1 and 2 give examples of individual concentration-time profiles simulated on the basis of Bayesian estimates of individual PK parameters obtained with the final model.

Figure 3 shows the plots of individual Bayesian estimates of clearance versus the age and WT of the breast cancer patients of studies VII and VIII. The line on the left panel is a population model prediction of the typical CL value as a function of age. The upper and lower lines on the right panel correspond to the model-predicted CL values typical for 50-year-old patient and for the oldest patient in the group (86 years), respectively. It is evident from Fig. 3 that the effect of WT is negligible, and the age effect explains only a minor part of the overall interindividual variability in CL.

The unexplained interindividual variability in CL was about 38%, which is substantially lower than the 50% value found after fitting of the preliminary model (without any fixed effect). There was an interoccasion variability of 18.5% (CV) in CL (studies VII and VIII), whereas that recorded for volumes of distribution and k_a was negligible (≤1%).

All three parameters reflecting VOR distribution in the body (Vc, Vp, and Q) were found to be proportional to WT. Besides this, there was a significant gender effect upon Vp, which also resulted in lower Vss values in men as compared with women (0.83 and 1.06 l/kg, respectively, as calculated using the typical Vc and Vp values). This effect could be detected only using data from the formal PK studies, which included subjects of both sexes. In Fig. 4 (left panel), estimates of individual Vss are plotted against WT, and almost all values recorded for women exceed those noted for men of the same or similar weight. Such a contrast might be attributable to the known higher fat content in women as compared

Table 2 Final estimates obtained for parameters of the VOR population PK model using the combined data set, which included data from the formal PK studies and clinical efficacy trials

Parameters	Description	Units	Estimate	SE in %
θ				
1	Basal CL in healthy volunteers (single dose)	l/h	8.64	4.3
2	Basal CL in patients (single dose)	l/h	4.82	5.9
3	Multiple-to-single dose CL ratio	–	0.758	4.0
4	CL in the subjects of study III relative to other studies	–	0.751	9.0
5	Rate of CL decrease with age after 50 years	l/h per year	0.0465	17.5
6	WT-normalized Vc	l/kg	0.425	4.1
7	WT-normalized Vp in males	l/kg	0.404	6.7
8	WT-normalized Vp in females	l/kg	0.635	3.1
9	WT-normalized Q	$l\ h^{-1}\ kg^{-1}$	0.171	4.7
10	k_a at multiple dosing	h^{-1}	1.78[a]	9.4[b]
11	k_a after a single dose	h^{-1}	2.93[a]	17.1[b]
ω				
1	Residual interindividual variability in CL (CV)	%	38.7	10.0
2	Residual interindividual variability in Vc (CV)	%	11.3	93
3	Residual interindividual variability in Vp (CV)	%	10.9	84
4	Residual interindividual variability in k_a (CV)	%	44.2[a]	39.8[b]
σ				
1	Residual variability in concentration: proportional error (CV)	%	28.0 (24.0)	7.9 (4.8)

[a] Parameters estimated using data from the formal PK studies only and fixed during fitting of the model to the combined data set
[b] Parameters estimated using data from the formal PK studies only

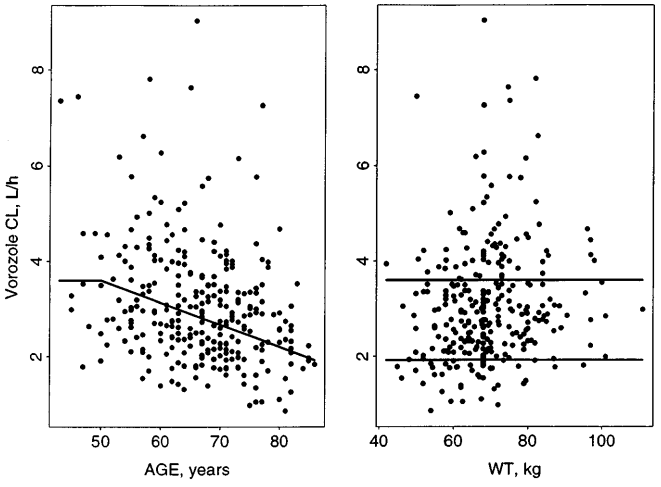

Fig. 3 Individual Bayesian estimates of VOR clearance obtained in patients from studies VII and VIII as plotted versus their age and WT. The population-model-predicted profile for the typical CL value as a function of age is shown *on the left*. The *upper and lower lines on the right* correspond to the model-predicted CL values typical for a 50-year-old patient and for the oldest patient in the group (86 years), respectively

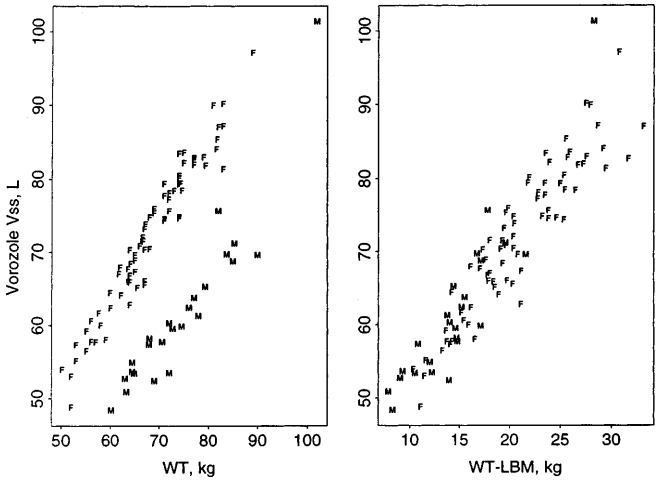

Fig. 4 Individual Bayesian estimates of VOR steady-state volume of distribution obtained in healthy volunteers as plotted versus their WT and WT-LBM difference. A symbol (*M*, *F*) used to identify each individual value shows the gender of the subject

with men. The latter could be approximated by the WT-LBM difference [2]. As can be seen in Fig. 4 (right panel), the two clusters of Vss values corresponding to men and women almost collapsed when they were plotted versus WT-LBM differences.

Among other PK parameters, the half-life is of importance for the clinical use of any drug and should be considered. Figure 5 clearly demonstrates that the $t_{1/2}$ of VOR is inversely proportional to CL and is not influenced by Vss. Thus, any factor reducing CL (e.g., age or multiple dosing) will automatically prolong the $t_{1/2}$.

Table 3 displays the median values recorded for Bayesian individual estimates of the most important PK parameters of VOR at steady-state for the patients of studies VII and VIII, split according to their age. This gives an idea of the actual magnitude of the age effect in absolute values.

Discussion

Population PK modeling plays an important role in the determination of demographic and other variables affecting PK parameters that may be of importance in

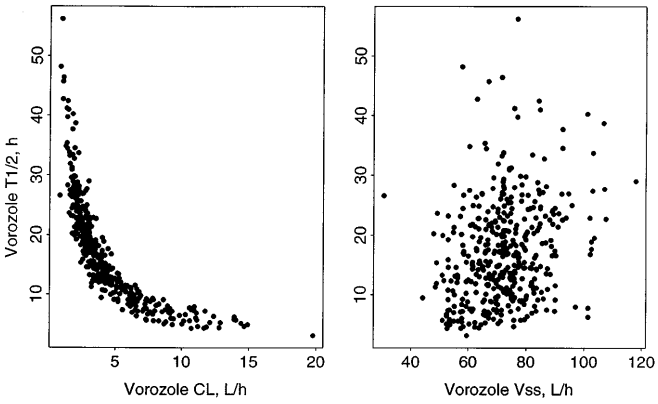

Fig. 5 Individual estimates obtained for the VOR half-life in all subjects who were included in the complete data set as plotted against VOR CL (*left*) and Vss values (*right*)

optimization of the drug dose. The NONMEM method is broadly used to build PK models that incorporate various covariates as fixed effects; however, this may be a complicated task, especially if many covariates and their combinations should be tested as potential determinants of structural PK parameters such as CL or volumes of distribution. In this work we used a method that consisted of exploratory graphical analysis of conditional (Bayesian) estimates of individual PK parameters generated by the NONMEM program after fitting of a model that contained only random effects (i.e., no covariate). This method is similar to those proposed by Maitre et al. [6] and Mandema et al. [7].

The major problem associated with this method is that it requires high-quality data, with a sufficient number of samples being taken from each subject to guarantee the closeness of Bayesian estimates to (unknown) true individual parameter values. Obviously, sparse clinical-efficacy trail data (such as those from our studies VII and VIII) are not suitable for this since a random variability may obscure any covariate effect. In such studies it is also difficult to ensure sufficiently uniform distribution of sampling times across the interdose interval; e.g., in study VIII it was generally near 24 h after the last intake (Fig. 2).

In the case of VOR, numerous formal PK studies were carried out in healthy volunteers of both sexes and in breast cancer patients after single administration and at multiple dosing. A considerable number of subjects were recruited (97) and the ranges of demographic covariates were broad enough (Table 1). The clinical trial data were combined with those from the formal PK studies only after the completion of the population model. The latter was fitted to the combined data to get the final estimates of fixed and random effect parameters.

VOR has been shown to be eliminated mainly by metabolism via CYP3A4 isozyme (unpublished results, Janssen Research Foundation). According to the results of the present analysis, the CL of oral VOR is low (less than 10% of the hepatic blood flow), and the presystemic elimination is presumably insignificant. A high degree of unexplained interindividual variability in CL may result from the intrinsic (mainly genetically determined) variability in CYP3A4 activity. The age-related decrease and the healthy volunteer/breast cancer patient differences in CL might at least partly be attributable to the reduced metabolic capacity in these patients as compared with the normal young subjects. The slightly lower CL observed at multiple dosing in comparison with single-dose administration could be explained by the effect of some VOR metabolite(s) accumulated in plasma during repeated administration.

The highly statistically significant fixed effect was the gender difference in volumes of distribution (see Figs. 4, 6), which could be related to the higher fat content in women as compared with men. Nevertheless, such a large gender difference is clinically irrelevant since (a) all patients are women and (b) the steady-state levels of VOR are determined primarily by CL.

The effect of age on the major VOR parameters recorded for breast cancer patients of studies VII and VIII, who were predominantly older than 50 years is illustrated by Table 3. As one can see, there is a 16% and a 30% decrease in CL in the groups of 61- to 75-year-old patients and 75-year-old patients, respectively. The $t_{1/2}$ is prolonged accordingly, whereas Vss remains almost constant. The $t_{1/2}$ is determined by the CL (Fig. 5), which is common for low-clearance drugs. The prolonged $t_{1/2}$ value recorded for VOR at multiple-dose administration (ca. 20 h, Table 3) may be of clinical benefit, since the plasma level will not drop too low even if a patient casually skips a dose.

In conclusion, both inter- and intraindividual variabilities in VOR PK, especially in CL, were found to be high, and healthy volunteer/patient, single/multiple dosing differences, and age were identified as the most important fixed effects influencing VOR CL. However, their inclusion in the model did not explain

Table 3 Median values recorded for the Bayesian estimates of individual VOR clearance, half-life, and steady-state volume of distribution in breast cancer patients of three age groups

Parameter	Range of age (years)				
	≤60 (n = 74)	61–75 (n = 162)		>75 (n = 50)	
	Value	Value	Percent change[a]	Value	Percent change[a]
CL (l/h)	3.30	2.77	–16.0	2.31	–30.0
$t_{1/2}$ (h)	17.4	20.1	15.5	22.9	31.6
Vss (l)	74.7	72.0	–3.6	71.5	–4.3

[a]As compared with the ≤60-year-old group

the major part of the interindividual variability, which is most probably genetically determined. The relatively weak effect of age on CL is unlikely to be clinically relevant.

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