

## Population Pharmacokinetic Analysis of Vancomycin in Patients with Hematological Malignancies

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**This study determines vancomycin (VAN) population pharmacokinetics (PK) in adult patients with hematological malignancies. VAN serum concentration data ( $n = 1,004$ ) from therapeutic drug monitoring were collected retrospectively from 215 patients. A one-compartment PK model was selected. VAN pharmacokinetics population parameters were generated using the NONMEM program. A graphic approach and stepwise generalized additive modeling were used to elucidate the preliminary relationships between PK parameters and clinical covariates analyzed. Covariate selection revealed that total body weight (TBW) affected  $V$ , whereas renal function, estimated by creatinine clearance, and a diagnosis of acute myeloblastic leukemia (AML) influenced VAN clearance. We propose one general and two AML-specific models. The former was defined by  $CL$  (liters/h) =  $1.08 \times CL_{CR(\text{Cockcroft and Gault})}$  (liters/h);  $CV_{CL} = 28.16\%$  and  $V$  (liters) =  $0.98 \times TBW$ ;  $CV_V = 37.15\%$ . AML models confirmed this structure but with a higher clearance coefficient (1.17). The a priori performance of the models was evaluated in another 59 patients, and clinical suitability was confirmed. The models were fairly accurate, with more than 33% of the measured concentrations being within  $\pm 20\%$  of the predicted value. This therapeutic precision is twofold higher than that of a noncustomized population model (16.1%). The corresponding standardized prediction errors included zero and a standard deviation close to unity. The models could be used to estimate appropriate VAN dosage guidelines, which are not clearly defined for this high-risk population. Their simple structure should allow easy implementation in clinical software and application in dosage individualization using the Bayesian approach.**

After nearly 4 decades of clinical use, vancomycin (VAN) has maintained an important and uncontested niche in the antibacterial arsenal owing to its consistent activity against almost all gram-positive bacteria (48). However, the emergence and gradually increasing prevalence of vancomycin-resistant organisms in recent years have led to its administration being limited to specific indications (8, 46).

The empirical use of VAN in persistently febrile neutropenic patients remains controversial (16, 46). Currently, the prevalent opinion is for a restrictive use of glycopeptides, i.e., only for patients whose infection requires them, based on the microbiological data and a rigorous clinical evaluation of the patient. From a practical standpoint, this postulate implies, first, a rational antibiotic selection based on potential pathogens and, second, optimal use, including the drug dose and duration of therapy (36). In this sense, the population approach and pharmacodynamic criteria have become available as tools in individualized antimicrobial therapy, leading to increased efficacy and reduced selection of resistance (13). In order to apply such a strategy in everyday clinical practice, the precise pharmacokinetic (PK)-pharmacodynamic index determining efficacy and its target value as well as population PK

parameters obtained from specific cohorts (oncology, intensive care unit, etc.) must be known or estimated (19, 40, 45).

A specific glycopeptide-treated population benefiting from this approach could be patients with hematological malignancies, owing to their high risk of developing life-threatening bacterial infections and the need for higher-than-expected dosages (9, 17, 34, 35). However, little is known about the VAN pharmacokinetics in these patients since only one population PK analysis has been published (17). The methodological and sampling size constraints of this work suggested the need for studies aimed at improving our knowledge about the PK behavior of this drug in this particular group of patients. Other populations of patients with nonhematological diseases, mainly pediatric, treated with VAN have been appropriately characterized using the most usual and suitable population approach of mixed-effect modeling implemented in the NONMEM program.

On this basis, the information obtained should provide specific PK parameters to estimate appropriate dosage guidelines, which are not clearly defined for this high-risk population.

### MATERIALS AND METHODS

**Patients and treatment.** Adult ( $\geq 15$ -year-old) inpatients with an underlying hematological malignancy admitted to the Hematology Unit of the University Hospital of Salamanca (Spain) from 1989 to 1999 on VAN therapy for suspected or documented infection caused by gram-positive bacteria were chosen retrospectively for the analysis. After a detailed examination of their medical reports (clinical history), some patients were excluded on the basis of two criteria: (i) the lack of the necessary data concerning the patients' demographic, physiopathological, and clinical status (11 patients) and (ii) hospitalization in the intensive care unit during VAN therapy (six patients). According to previous criteria, a

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total of 348 treatments corresponding to 274 patients were available. Owing to intraindividual physiopathological changes, if the time period between two successive treatments in the same patient was more than 1 month we considered each as an individual course of VAN for population analysis, according to our previous experience for this kind of patient (37). Two hundred twenty-four patients received only one course of VAN therapy, and the remaining 50 patients received from two to six courses. Informed consent and ethical approval were unnecessary because the study involved a retrospective collection of routine clinical data coming from therapeutic drug monitoring (TDM). However, since additional patient information was needed for this study, approval was obtained from the Institutional Review Board of the University Hospital of Salamanca.

Initial VAN dosage regimens were chosen by attending physicians according to a specifically designed nomogram for hematological patients, taking into account the patients' age, weight, and renal function (17). VAN was administered by intermittent intravenous infusion over 0.5 to 1 h at doses ranging from 200 to 3,900 ( $1,535 \pm 280$ ) mg/day, the dosage interval ranging from 6 to 48 h.

**Data acquisition.** PK data were collected in a database by the clinical pharmacokinetic service of our hospital. Dosing and sampling times were always recorded by nursing staff. The accuracy of the records was further assessed by a clinical pharmacist belonging to the clinical pharmacokinetic service.

From these PK reports, the following data were obtained: patient identification, TDM dates, and the characteristics of VAN therapy. On the day of each VAN TDM, the following data were retrieved from the patients' medical records: age, weight, body surface area, serum creatinine ( $S_{CR}$ ), hemoglobin, albumin, and time postchemotherapy. The categorical variables collected were gender (GEN); hematological diagnosis; Eastern Cooperative Oncology Group (ECOG) performance status according to the standards of the Eastern Cooperative Oncology Group (15); stage of antineoplastic treatment; and the presence or absence of autologous bone marrow grafting, neutropenia (absolute neutrophil count of  $<500/\text{mm}^3$ ), and hypoalbuminemia (serum albumin concentration of  $<3.5$  g/dl). Concurrent antibiotic therapy with amikacin and amphotericin was also recorded. Creatinine clearance ( $CL_{CR}$ ) was estimated as a function of individual variables such as total body weight (TBW), height, age, body surface area, GEN, and  $S_{CR}$ . Estimations following the formulas of Cockcroft and Gault (10), Jelliffe (23), Tsubaki et al. (44), and Levey et al. (27) were made for each patient.

According to statistical criteria (power of 0.8) and desired clinical representativeness we selected a minimum number of 200 patients to build the model (index set). To obtain this figure, a period of approximately 7 years (30 patients/year) was necessary, and to externally validate the model another 50 patients (validation set) were required. Patient assignment to the index and validation groups was chronological (three-fourths and one-fourth of the evaluated time, respectively). Data acquisition for the validation set was accomplished after the final population analysis, so only significant covariates were recorded. To prevent the potential introduction of bias into the prediction analysis, only two items of VAN serum data per patient were obtained in the validation group.

Table 1 summarizes the demographic and clinical characteristics of the patients included in the study.

**Serum sampling and drug analysis.** Blood sampling was ordered as required clinically. Thus, one or more postdistribution serum samples after the first doses or at steady state are usually drawn, but other sampling times could be used if recorded accurately. Figure 1 gives details on the distribution of concentrations with respect to the number of doses and sampling times.

Fluorescence polarization immunoassay (TDx; Abbot Laboratories, North Chicago, IL) was used for drug analysis. The quantification limit of the assay for VAN was 0.6 mg/liter, and the intra- and interassay coefficients of variation (CV) were  $<5\%$  over the entire calibration range (7 to 75 mg/liter). Concentrations at or below the quantification limit of the assay were recorded as undetectable in the patient report and hence were not considered in the analysis.

**Pharmacokinetic and statistical analysis.** (i) **Pharmacokinetic modeling.** A population PK method based on a nonlinear mixed-effect modeling approach was used (NONMEM program, version V; double precision, level 1.1) (4). The first-order conditional estimation was used throughout. To determine the most suitable compartmental model, we first fitted data for VAN concentrations versus time to both one- and two-compartment models, with first-order elimination, specified to NONMEM by ADVAN1-TRANS2 or ADVAN3-TRANS4 routines, respectively. The fixed-effect PK parameters estimated directly with these model specifications were total body clearance (CL) and distribution volume ( $V$ ) for the former and CL, distribution volume of the central compartment ( $V_1$ ), intercompartment clearance, and distribution volume of the peripheral compartment ( $V_2$ ) for the latter. Bayesian PK estimates for individual subjects were obtained by specification of the POSTHOC option to NONMEM.

Both additive and exponential-error models were tested to describe interindi-

TABLE 1. Demographic and clinical data of the patient population

Variable	Index set	Validation set
No. of patients (male/female)	215 (119/96)	59 (40/19)
No. of serum concns measured	1,004	124
Age (yrs)	$51.5 \pm 15.9$	$51.4 \pm 16.9$
Wt (kg)	$64.7 \pm 11.3$	$67.1 \pm 12.1$
Body surface area ( $\text{m}^2$ ) <sup>a</sup>	$1.7 \pm 0.2$	$1.7 \pm 0.2$
Serum creatinine (mg/dl)	$0.9 \pm 0.4$	$1.0 \pm 0.5$
Creatinine clearance (ml/min) <sup>b</sup>	$89.4 \pm 39.2$	$89.6 \pm 42.5$
Serum albumin (g/dl)	$3.4 \pm 0.9$	
Time postchemotherapy (days)	$12.7 \pm 12.8$	
Daily dose (mg/day)	$1,535 \pm 280$	$1,555 \pm 214$
VAN serum concn (mg/liter)	$9.1 \pm 8.0$	$10.1 \pm 6.1$
No. of serum data per patient	$3.5 \pm 1.9$	2
Frequency (%)		
Hematology diagnosis		
AML	27.6	40.3
NHL (non-Hodgkin's lymphoma)	30.8	30.6
ALL (acute lymphoblastic leukemia)	8.0	1.6
CML (chronic myeloid leukemia)	8.0	6.4
CLL (chronic lymphoid leukemia)	4.2	1.6
Hodgkin's disease	7.7	1.6
Myelodysplastic syndrome	4.5	12.9
Multiple myeloma	4.2	3.2
Other	4.9	1.6
Autologous bone marrow transplant	15.7	
Neutropenia	43.7	
ECOG <sup>c</sup> (0, 1, 2)/(3, 4)	45.1/12.9	
Concomitant drug		
Amikacin	38.8	
Amphotericin	21.0	

<sup>a</sup> Estimated according to the equation of Mosteller (31).

<sup>b</sup> Estimated according to the equation of Cockcroft and Gault (10).

<sup>c</sup> Performance status is graded from 0 to 4 according to the standards of the ECOG (15).

vidual variability:  $\theta_j = \theta' + \eta_{\theta j}$  and  $\theta_j = \theta' \exp(\eta_{\theta j})$ , where  $\theta_j$  is the estimate for a PK parameter in the  $j$ th individual as predicted by the model,  $\theta'$  is the population mean of the PK parameter, and  $\eta_{\theta j}$  represents the random variable with zero mean and variance  $\omega^2$ . Covariance was also estimated. It should be noted that the first-order method used in this analysis approximates the exponential error model as a proportional error model. The terms for interindividual variability were included only for CL,  $V$ , and  $V_1$ .

Residual variability, including intraindividual variability, measurement error, and model misspecification, was estimated using both additive and exponential error models:  $C_{ij} = C'_{ij} + \epsilon$  and  $C_{ij} = C'_{ij} \exp(\epsilon)$ , where  $C_{ij}$  and  $C'_{ij}$  are the observed and predicted VAN concentrations for the  $j$ th individual at time  $i$ , respectively, and  $\epsilon$  is the additive error (with zero mean and variance  $\sigma^2$ ).

(ii) **Model building.** Assumptions about the population model (one versus two compartments and additive versus exponential error models) were evaluated according to the objective function value (OFV) produced by NONMEM, which was the first criterion of selection. The Akaike criterion (2) and visual inspection of the distribution of weighted residual plots were also used.

To elucidate the preliminary relationships between a PK parameter obtained using a Bayesian maximum a posteriori estimation and covariates, a graphic approach to exploratory data analysis and the stepwise generalized additive model (GAM) implemented in Xpose were used (24).

Inclusion of a fixed-effect parameter in the basic model quantifies the relationship between a PK parameter and a covariate and allows it to be known whether that covariate significantly improves the ability of the model to predict the observed concentration-time profile. The OFV difference between two hierarchical models is asymptotically  $\chi^2$  distributed, with degrees of freedom (df) equal to the difference in the number of parameters between the two models, and should be at least 3.84 (if  $df = 1$ ) in order to achieve the desired level of significance of  $\alpha = 0.05$ . Other diagnostic criteria for the retention of a covariate in the model were a reduction in unexplained interindividual variability for the associated PK parameter; an improvement in the graphic diagnostic model, evaluated by randomly distributed weighted residuals; a closer relationship between predicted and observed concentrations; and the criterion that the 95% confidence interval, estimated using standard errors, should not include zero value. Additionally, the percent estimation error of fixed and random parameters should not be higher than 25 and 50%, respectively (3). The full model thus generated was then subjected to backwards elimination, where each model pa-

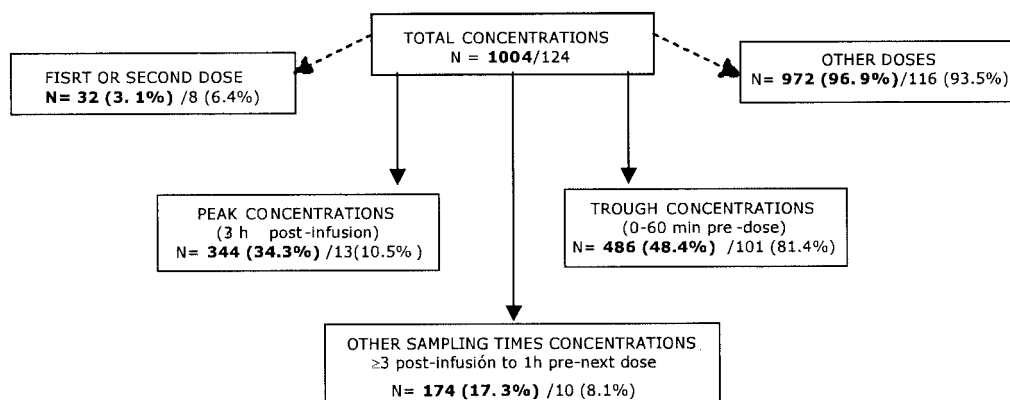


FIG. 1. Distribution of VAN concentrations in relation to the number of doses and sampling times in the index (boldface) and validation data sets.

parameter was fixed to zero value, using a more stringent criterion of statistical significance ( $\alpha = 0.01$ ).

(iii) **Validation of the population pharmacokinetic model.** The population parameters obtained with the index data set were used to estimate values with NONMEM individual parameters in the validation data set. From these individual parameters, a priori (i.e., without individual serum data) VAN serum concentrations were estimated (the “simul” NONMEM option) at the same times as those actually observed and compared in order to know their predictive performance according to standard procedures (42).

Additionally, standardized prediction errors were estimated in order to evaluate whether the regression model was correct and the parameters estimated were unbiased (47). The clinical suitability of the predictions was defined as the percentage of attainment within  $\pm 20\%$  of the predicted value.

The ADAPT II software (11) was used for Monte Carlo simulation of 1,000 subjects in order to graphically delineate variability in VAN pharmacokinetic profile for a standard dosage. For patients with the typical mean characteristics of the population studied (TBW = 65 kg and  $CL_{CR} = 90$  ml/min), receiving a dose of 1,000 mg/12 h administered in 60-min intermittent infusions, simulations were performed using the mean parameter vector and covariance matrices estimated with the models selected.

In order to visually compare the VAN pharmacokinetic profiles, graphic simulations were performed with Pharmacokinetics System software, as described previously (1, 18, 32, 33, 49, 52).

Summary statistics and differences between the index and validation groups were obtained with the SPSS program (v. 10.0.7) (43).

## RESULTS

As reflected in Table 1, the index and validation groups were comparable with respect to the demographic and clinical characteristics, except for the higher percentage of women and acute myeloblastic leukemia (AML) diagnoses in the validation group. The chronological criterion for assigning the patients to the index and validation groups explains the difference between the numbers of measured serum levels per patient because the VAN TDM guidelines concerning sampling times had changed during this time period, changing focus from peak/trough to only trough data.

Comparison of the one- and two-compartment models according to the diagnostic criteria specified above in Materials and Methods revealed a slightly lower value of the OFV for the latter model (4,502.68 versus 4,495.44). However, there were no obvious differences in the scatter plots between the two models, and the Akaike criterion (2) was better for the simpler model (8,462.46 versus 8,454.46). Additionally, the mean parameter values obtained with the two-compartment model were unrealistic for both the central and peripheral distribu-

tion volumes (50.4 and 100.0 liters, respectively). Accordingly, the one-compartment model was assumed to adequately describe serum VAN concentrations in view of the good correlation between the individual predicted and measured concentration data ( $r = 0.943$  and no statistical differences with the identity line as reflected by the 95% confidence interval of the constant,  $-0.59$  to  $0.09$ , and slope,  $0.98$  to  $1.02$ ). In this model, the interindividual and residual errors were best described by exponential and additive structures, respectively. The population parameters estimated for this model are depicted in Table 2. A striking observation is the large estimation error in the CV on  $V$ . Since the data analyzed were obtained mostly at steady state, it is not surprising that the estimates pertaining to interindividual variability in  $V$  are less precise and more biased than those pertaining to clearance. The covariate analysis was then examined on the basis of this structural model.

According to graphic and GAM preliminary analysis with covariates measured directly, only four of them exhibited an evident influence in  $CL$  (TBW, GEN, age, and  $S_{CR}$ ) and  $V$  (TBW and  $S_{CR}$ ). When  $CL_{CR}$  (estimated individually from the Cockcroft and Gault equation [10], using the above-measured covariates) was analyzed, it proved to be the most significant VAN pharmacokinetics predictor. Once  $CL_{CR}$  was identified as the only significant covariate with an effect on VAN clearance, the influence of several estimation methods for this renal function index was tested. Higher OFVs were obtained with the Jelliffe (4,037) and Levey (4,043) formulas (23, 27) than with the Cockcroft and Gault (4,025) and Tsubaki (4,023)

TABLE 2. Population pharmacokinetic parameters of VAN estimated from the basic model

Parameter <sup>a</sup>	Estimate	Estimation error <sup>b</sup> (%)
$CL$ (liters/h) = $\theta_1$	4.62	4.50
$V$ (liter) = $\theta_2$	67.8	24.19
$\omega_{CL}$ (%)	44.38	12.33
$\omega_V$ (%)	38.34	134.69
$\omega_{CL/\omega_V}$ (%)	26.87	25.07
$\sigma$ (mg/liter)	4.08	12.13

<sup>a</sup>  $\theta$ 's, parameters expressing  $CL$  and  $V$  (see text);  $\omega$  and  $\sigma$ , parameters expressing interindividual and residual variabilities, respectively (see text);  $\omega_{CL}/\omega_V$ , parameter expressing covariance.

<sup>b</sup> Expressed as a coefficient of variation.

TABLE 3. Summary of principal covariate models tested in population model building (one-compartment structure)<sup>a</sup>

Model no. and description	OFV	CV <sub>CL</sub> (%)	CV <sub>V</sub> (%)	σ (mg/liter)	Comment(s)
1. CL = θ <sub>1</sub> ; V = θ <sub>2</sub>	4,502.68	44.4	38.3	4.08	Basic model
2. CL = (θ <sub>1</sub> × TBW) × (S <sub>CR</sub> <sup>0.87</sup> ) × (age <sup>0.49</sup> ) × (1 + θ <sub>5</sub> × GEN); V = (θ <sub>2</sub> × TBW) × (1 + θ <sub>6</sub> × GEN)	4,044.08	30.1	37.9	3.47	Model suggested by GAM analysis
3. CL = θ <sub>1</sub> + θ <sub>3</sub> × CL <sub>CR</sub> ; V = θ <sub>2</sub> × TBW	4,025.91	27.5	37.1	3.52	Model 2 simplification; unacceptable estimation error and the 95% CI <sup>b</sup> included zero for θ <sub>1</sub>
4. CL = θ <sub>1</sub> × CL <sub>CR</sub> ; V = θ <sub>2</sub> × TBW	4,038.39	28.1	37.1	3.52	Final model selected. Additional criteria (see Materials and Methods) were also considered for the decision
5. CL = θ <sub>1</sub> × CL <sub>CR</sub> × (1 + θ <sub>3</sub> × AML); V = θ <sub>2</sub> × TBW	4,015.02	27.3	37.5	3.52	High estimation error for θ <sub>3</sub>

<sup>a</sup> θ's, parameters expressing CL and V as a function of covariates (see text); CV and σ, parameters expressing interindividual and residual variabilities, respectively (see text).

<sup>b</sup> CI, confidence interval.

equations (10, 44). Thus, the conventional Cockcroft method was selected because the latter, despite its specific design for oncologic patients, is merely a transformation of the former.

Table 3 summarizes the main models tested with NONMEM according to this preliminary analysis. The proposed final VAN population model, summarized in Table 4, is defined by the following relationships: CL (liters/h) = 1.08 × CL<sub>CR</sub>(Cockcroft and Gault) (liters/h); CV<sub>CL</sub> = 28.16% and V (liters) = 0.98 × TBW; CV<sub>V</sub> = 37.15%; σ = 3.52 mg/liter.

The influence of AML diagnosis on VAN pharmacokinetics was first assessed by graphic analysis. Although no particular trend emerged, its influence was formally assessed by inclusion as a covariate on CL. A significant reduction in the OFV was obtained, but the estimation error of associated θ was unacceptable (34.5%) and therefore this covariate was removed from the model. However, in view of (i) these results, (ii) the above-discussed limitation of NONMEM in detecting nonnormal distributions, (iii) the suspicion of a modified kinetic profile in leukemic patients, and (iv) the availability of a significant proportion of AML patients (*n* = 79), we decided to characterize VAN kinetics behavior specifically in this subpopulation. In AML patients the variables accounting for CL<sub>CR</sub> (TBW, GEN, age, and S<sub>CR</sub>) were better VAN clearance predictors than CL<sub>CR</sub> (OFV difference = 14.56, *P* < 0.01). However, other diagnostic criteria (lower unexplained variability and parameter estimation errors) as well as the presumed greater use of CL<sub>CR</sub> in clinical practice supported the exchangeability with

respect to an alternative simplified model, which included only this later covariate. The equations defining such population models, designated AML-1 and AML-2, were as follows: AML-1, CL (liters/h) = 0.49 × TBW × S<sub>CR</sub><sup>0.87</sup> × age<sup>-0.49</sup>; CV<sub>CL</sub> = 23.3%; CL was multiplied by 1.08 if the patient was male; V (liters) = 1.06 × TBW; CV<sub>V</sub> = 24.2%; σ = 3.25 mg/liter; AML-2, CL (liters/h) = 1.17 × CL<sub>CR</sub>; CV<sub>CL</sub> = 21.6%; V (liters) = 0.97 × TBW; CV<sub>V</sub> = 24.8%; σ = 3.20 mg/liters.

**Validation.** A priori predicted VAN concentrations in the validation data set from the proposed general population model afforded a mean prediction error of 0.82 ± 4.83 mg/liter. The bias for the AML-1 and AML-2 models was 1.95 ± 4.48 mg/liter and 0.33 ± 4.11 mg/liter, respectively. The predictive performance of the models was also evaluated by calculating the mean and standard deviation of the standardized prediction errors. The values obtained were 0.13 ± 1.47 mg/liter, 0.33 ± 1.26 mg/liter, and -0.04 ± 1.39 mg/liter for the general, AML-1, and AML-2 models, respectively. The 95% confidence interval included a zero value for all of them, and standard deviations were close to unity, which are necessary conditions for a model to be considered acceptable. The proportion of measured concentrations predicted accurately was 37.9, 33.3, and 39.6% for the general, AML-1, and AML-2 models, respectively.

## DISCUSSION

Despite the frequent administration of VAN in oncologic patients, standard dosage regimens continue to be used, although they may often be suboptimal owing to the greater CL and V values found in this target population (17, 34, 35). This, together with the reduced postantibiotic effect seen in neutropenic patients, could lead to unfavorable outcomes in this high-risk population.

Understanding the variability associated with pharmacokinetics and identifying subpopulations with special features can provide clinicians with relevant information for dosage individualization. Since no precise evaluation of VAN population PK exists for patients with hematological malignancies, we designed this study to characterize PK parameters, the covariates affecting their variability, and unexplained residual and

TABLE 4. Population pharmacokinetic parameters of VAN estimated from the final model

Parameter <sup>a</sup>	Estimate	Estimation error <sup>b</sup> (%)
θ <sub>1</sub> (liters/h)	1.08	2.12
θ <sub>2</sub> (liters/kg)	0.98	7.43
ω <sub>CL</sub> (%)	28.16	14.75
ω <sub>V</sub> (%)	37.15	48.12
ω <sub>CL</sub> /ω <sub>V</sub> (%)	23.12	31.61
σ (mg/liter)	3.52	15.12

<sup>a</sup> θ<sub>1</sub>, coefficient of CL<sub>CR</sub> on CL; θ<sub>2</sub>, coefficient of TBW on V; ω and σ, parameters expressing interindividual and residual variabilities, respectively (see text); ω<sub>CL</sub>/ω<sub>V</sub>, parameter expressing covariance.

<sup>b</sup> Expressed as a coefficient of variation.



TABLE 5. One-compartment pharmacokinetic parameters (mean  $\pm$  standard deviation) of VAN from different studies versus this study (boldface)

<i>n</i>	Type of patient	Age (yrs)	TBW (kg)	CL <sub>CR</sub> (ml/min)	CL (ml/min)	<i>V</i> (liters/kg)	Reference
11	Serious systemic infections	46.5 $\pm$ 16.6	67.8 $\pm$ 5.2	87.6 $\pm$ 22.3	62.7 $\pm$ 25.3	0.72 $\pm$ 0.35	29
50	Various MRSA infections <sup>a</sup>	37.3 $\pm$ 11.6	70.3 $\pm$ 16.0	76.9 $\pm$ 41.0	61.9 $\pm$ 22.3 <sup>c</sup>	0.55 $\pm$ 0.19	39
22	Adult inpatients	52.4 $\pm$ 14.7	71.0 $\pm$ 23.8	97.4 $\pm$ 35.7	79.2 $\pm$ 34.2	0.54 $\pm$ 0.22	6
704	From level 1 trauma center	44.5 $\pm$ 15.9	73.2 $\pm$ 17.2	80.2 $\pm$ 34.4	78.9 $\pm$ 37.1	0.64 $\pm$ 0.26	14
330	Leukemic and others <sup>b</sup>	47 (12–87)	71 (37–130) <sup>c</sup>	103 (21–273) <sup>c</sup>	95.8 <sup>e</sup>	0.75 $\pm$ 0.27	28
15	Prophylaxis before bypass surgery	60 $\pm$ 9	79 $\pm$ 12	82 $\pm$ 27.1	78.3 $\pm$ 32.6 <sup>d</sup>	0.65 $\pm$ 0.15 <sup>e</sup>	25
107	Medical/surgical in acute care hospital	53.4 $\pm$ 17.2	77.1 $\pm$ 23.1	89.5 $\pm$ 28.6	79.5 $\pm$ 33.3	0.6 $\pm$ 0.2	38
<b>215</b>		<b>51.5 <math>\pm</math> 15.9</b>	<b>64.7 <math>\pm</math> 11.3</b>	<b>89.4 <math>\pm</math> 39.2</b>	<b>96.5 (<math>\pm</math> 27.19)<sup>f</sup></b>	<b>0.98 (<math>\pm</math> 0.36)<sup>f</sup></b>	

<sup>a</sup> Primarily pneumonia and endocarditis. MRSA, methicillin-resistant *Staphylococcus aureus*.

<sup>b</sup> Sixty-five percent of patients were leukemic, and the other patients were from other clinical units.

<sup>c</sup> Ranges of values are shown in parentheses.

<sup>d</sup> Model-independent estimate.

<sup>e</sup> Estimate from  $V \times k_{el}$  (elimination rate constant).

<sup>f</sup> Standard deviation estimated from CV.

interindividual variabilities. Sparse VAN serum concentration data obtained from routine monitoring were used to estimate the population parameters. Limited sample acquisition in the clinical setting usually permits only one-compartmental models, although it is well accepted that VAN PK characteristics are more realistically described by a two-compartment model. However, in spite of the poor design these TDM data can provide results more representative of the population studied if a large number of patients are analyzed. All samples for VAN peak concentrations were drawn at least 2 hours after the end of the infusion, so the data are one compartment in nature. The available information did not allow the distributive phase to be described adequately.

The mean values (expressed in a homogeneous system of units to allow comparisons) obtained for VAN clearance and *V* in this study using NONMEM (1.19 ml/min/kg of body weight and 1.05 liters/kg) are slightly higher than the values reported in other studies using standard approaches (two-stage methods with a one-compartment model) in other adult populations (6, 7, 14, 25, 28, 29, 38, 39). Also, the mean values accounting for the effect of renal function and TBW on VAN clearance and *V*, respectively, were higher than the ranges quoted for this antibiotic in other adult populations (26, 30, 50). The greater volume of distribution observed can be attributed to the pathophysiology of malignancy, although postdistribution sampling times and the one-compartment pharmacokinetic model used in the analysis could also have been responsible. For the purposes of comparison, the one-compartment pharmacokinetic parameters from different studies are summarized in Table 5. The magnitude of the differences (26 to 42%) is the main argument against the use of pharmacokinetic data from the general population instead of from the population of interest.

Our results point to general rather than population-specific covariates as predictors of the VAN pharmacokinetic parameters. Thus, critical characteristics of patients with hematological malignancies such as diagnosis, severity of the disease, the time postchemotherapy, the stage of antineoplastic treatment, and the existence of neutropenia or a bone marrow graft (among other clinical parameters analyzed) had no significant correlation with or effect on VAN disposition. Only age, TBW, *S*<sub>CR</sub>, and GEN proved to have a significant effect on the PK parameters (model 2 in Table 3), as would be expected in a

drug eliminated mainly through renal excretion. Owing to the inclusion of these covariates in the usual index of renal function, CL<sub>CR</sub>, the population model could be simplified by including this latter variable instead of the former ones (model 4 in Table 3). In fact, this simplified model significantly improved ( $P < 0.05$ ) the data fit and revealed a structure similar to those reported in other population analyses with this drug (50, 51).

To our knowledge, no previous VAN studies using NONMEM have been conducted specifically with patients with hematological malignancies, which hinders critical comparison of our results with others. For this antibiotic, five studies using mixed-effect models have been published previously (21, 22, 41, 50, 51). Methodological issues (patient age, sample size, and PK analysis) mean that only one of them (50) can be compared with our final model. This comparison revealed that the coefficients of the linear relationship between CL and CL<sub>CR</sub> (1.08) and *V* (0.98) in our model were greater than those obtained by those authors, suggesting enhanced VAN clearance and *V* in patients with hematological malignancies. Such notions are consistent with those reported for aminoglycoside antibiotics in the same kind of patients (5, 12, 33, 53). The underlying mechanism explaining enhanced disposition in this patient population could be related to two hypotheses: possible changes in renal function induced by the cancer and the fact that CL<sub>CR</sub> is a surrogate index of the glomerular filtration rate, although the tubular secretion of VAN should at least partially contribute to its renal excretion (20).

Figure 2 shows mean VAN profiles in a standard patient (male, 65 kg in weight, with a CL<sub>CR</sub> of 90 ml/min, receiving a conventional dosage regimen of 1,000 mg/12 h) simulated according to the population models developed in this study versus a general model for the adult population (1). The significantly lower serum concentrations predicted with our models in hematological patients owing to the higher *V* and CL values estimated are noteworthy. According to our final model, a typical patient would require a mean dosage of 45 mg/kg/day (50% higher than that conventionally used) in order to attain an area under the curve of 500 mg/liter  $\cdot$  h. Dosage intervals of 6, 8, or 12 h can be used depending on desired fluctuations in serum levels. Dosage recommendations based on peak target concentrations should be adapted to the one-compartment model as we have previously

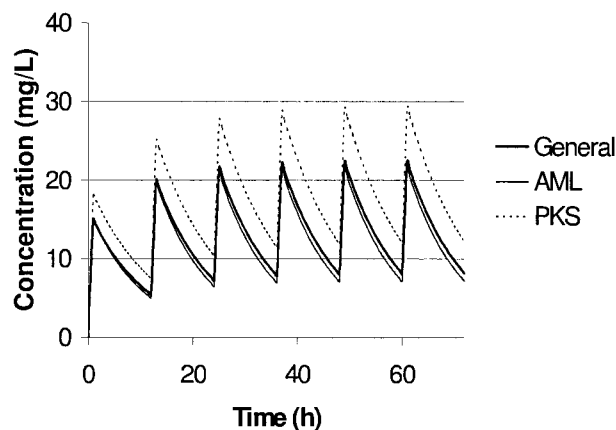


FIG. 2. Simulated mean VAN serum profiles in a standard patient (male, 65 kg, 50 years old, with a  $CL_{CR}$  of 90 ml/min, receiving 1,000 mg/12 h), according to two population models developed in this study (general model for patients with hematological malignancies and model customized for AML diagnosis) in comparison with the one-compartment model implemented in the AbbottBase Pharmacokinetics System software (PKS) for adult populations.

established (18). Such a target should be 19 to 21 mg/liter as opposed to the generally cited 30 to 40 mg/liter.

The interindividual variability of VAN clearance decreased from 44.4% in the basic model to 28.2%, while in  $V$  no significant reduction was apparent in the final model proposed. Residual variability decreased by only 14% between the basic and final models; such variability corresponded in the latter to 11.7% and 35.3% for VAN serum concentration values of 30 and 10 mg/liter, respectively. Thus, the unexplained variability accounted for by our model remains significant, probably due to the heterogeneity of the population studied. In our opinion, the greater physiopathological homogeneity, the greater representativeness owing to the hematological diagnosis of AML, and the trend shown by this diagnosis in VAN clearance justify the building of a specific model for this subpopulation. The models selected in AML patients (AML-1 and AML-2) confirm the influence of the same covariates and the structure of the final model defined for the whole population. Moreover, as

expected, the interindividual and residual variabilities are reduced in these AML models. The coefficient of the relationship between VAN clearance and  $CL_{CR}$  (model AML-2) involves a 10% additional increase of CL in patients with AML with respect to the general final model for patients with hematological malignancies. No appreciable AML-dependent changes in  $V$  were observed, although the interindividual variability of this parameter was significantly lower than that estimated by the general model (24.2% versus 37.1%).

The main results obtained in population PK analysis and their interpretation are dependent on the study design. Critical factors are the total number of patients, the representativeness of the covariates analyzed, and sampling strategies. The population models, both general and AML specific, constructed from the analysis of 1,004 and 301 VAN serum samples, respectively, underscore the representativeness of our sample of patients and broaden the generality of our results to similar hematological populations. However, previous validation is necessary to certify their reliability and appropriateness for the target population receiving this drug. The results obtained for external validation in a subset of 59 (24 with AML diagnosis) patients confirmed the good predictive performance of our models and suggest that they would constitute a useful clinical tool for a priori individualizing VAN therapy. Moreover, more than one of three (37.9%) a priori predictions lies within  $\pm 20\%$  of the predicted concentrations. This therapeutic precision seems to be more than twofold for this model in comparison with a general model implemented in the AbbottBase Pharmacokinetics System software (16.1%). It is clear that having an a priori dosing method achieving target concentrations without bias and as close as those desired is an important issue when TDM is controversial. In fact, the more reliable the dosing method, the less TDM that is required. However, as seen in Fig. 3 for the general and AML-2 models, the magnitude of the interindividual and residual variabilities involves a broad range of expected VAN serum concentrations for a fixed-dosage regimen, which could justify TDM of this drug in hematological patients.

To translate these data into clinically useful information in order to improve the outcome of VAN therapy, it should be

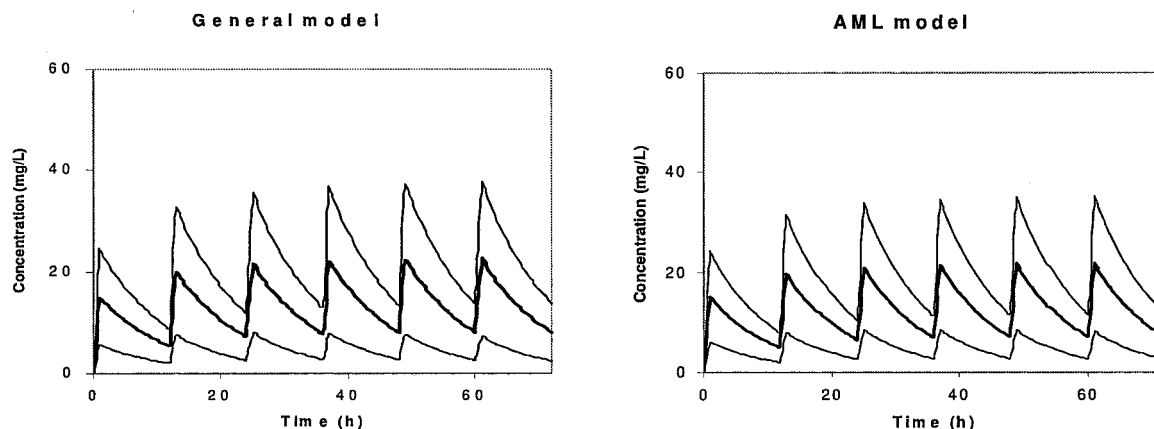


FIG. 3. Typical (thick line) vancomycin population profiles including interindividual plus residual variabilities (thin lines) from the general and AML-2 models for a standard patient (male, 65 kg, 50 years old, and with a  $CL_{CR}$  of 90 ml/min) receiving 1,000 mg/12 h.

emphasized that the simple structure of the models developed allows easy implementation in clinical PK software and their application in dosage individualization using the Bayesian approach. Strictly, this approach can be used only if an adequate PK model for the specific population treated and routine drug monitoring in VAN therapy are available.

In conclusion this study proposes and validates VAN pharmacokinetic models specifically designed for patients with hematological malignancies in general and customized for AML patients in particular. Although these models will be useful for initial dosage selection and Bayesian forecasting of VAN therapy, our proposals should be evaluated prospectively in comparison with alternative models (i.e., nomograms specifically derived for this patient population) and should be correlated with clinical and microbiological outcomes to determine their relevance in clinical practice.

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