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Tobramycin disposition in ICU patients receiving a once daily regimen: population approach and dosage simulations

Jean-Marie Conil,[1,2] Bernard Georges,[1,2] Stéphanie Ruiz,[1] Thomas Rival,[1] Thierry Seguin,[1] Pierre Cougot,[1] Olivier Fourcade,[1,2] Georges Houin Pharmd[3] & Sylvie Saivin[2,3]

[1]Pôle d'Anesthésie-Réanimation, Hôpital de Rangueil, 31059 Toulouse Cedex 9, [2]GRCB 48, IFR 150 Institut Fédératif de Recherche Biomédicale de Toulouse, Université Toulouse III Paul Sabatier, 31062 Toulouse Cedex 9 and [3]Laboratoire de Pharmacocinétique et Toxicologie Clinique, Institut Fédératif de Biologie, 31059 Toulouse Cedex 9, France

Correspondence
Dr Sylvie Saivin, Laboratoire de Pharmacocinétique et Toxicologie Clinique, Institut Fédératif de Biologie, TSA 40031, 330, avenue de Grande Bretagne, 31059 Toulouse Cedex 9, France.
Tel.: + 33 5 6769 0367
Fax: + 33 5 6769 0384
E-mail: saivin.s@chu-toulouse.fr

Brief summary statement: A tobramycin population pharmacokinetic model was qualified in intensive care unit patients after a once daily dose. Based on simulations, dosage regimens are recommended as a function of patient height and Cockcroft creatinine clearance.

Keywords
ICU patients, population pharmacokinetics, tobramycin

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT?

- It is well known that tobramycin given as an once daily dose according to the usual recommendations needs therapeutic drug monitoring by measurement of peak and trough concentrations. In the literature, there are only few published studies on the population pharmacokinetics of once daily tobramycin in critically ill patients. Glomerular filtration rate and bodyweight were identified as covariates contributing to the inter-individual variability in the disposition of aminoglycosides. The study, by Peris-Marti *et al.* [24], only evaluated the pharmacodynamic effectiveness of a 4 mg kg^{-1} dose of tobramycin given once daily in critically ill patients. The authors concluded with a simulation showing that for a theoretical MIC of 1 or 2 mg l^{-1}, a 7 mg kg^{-1} dose was required.

WHAT THIS STUDY ADDS?

- Our results confirm the high variability of tobramycin disposition in intensive care patients and consequently the possible lack of effectiveness.
- By using a population pharmacokinetic approach, two explicative covariates (height and Cockcroft creatinine clearance) added to a two-compartment model with proportional error, explained much of the inter-individual variability of tobramycin disposition in the critically ill patient population.
- In a median ICU patient, simulations were performed at various dosage regimens and peak and AUC pharmacodynamic targets could not be reached simultaneously in more than 45% of the ICU patient population. Drug monitoring is required to manage efficacy and toxicity.

AIM

The aim of this study was to evaluate the disposition of tobramycin (TOB) in critically ill patients (ICU) by a population pharmacokinetic approach, to determine the covariates involved, and to simulate tobramycin dosage regimens.

METHODS

Forty-nine adult ICU patients received TOB (5 mg kg^{-1}) once daily. NonMem modelling was performed on 32 patients. The 17 other patients were used for the qualification process by normalized prediction distribution error. Then Monte Carlo simulations (MCS) were performed.

RESULTS

A two-compartment model with a proportional error best fitted the data. TOB total clearance (CL_{TOB}) was significantly correlated with Cockcroft creatinine clearance (COCK) and height. TOB clearance was 4.8 $\pm$ 1.9 l h^{-1} (range 1.22–8.95), the volume of distribution of the central compartment was 24.7 $\pm$ 3.7 l (range 17.34–32.83) and that of the peripheral compartment and the inter-compartmental clearance were 30.6 l and 4.74 l h^{-1}, respectively. Only 29% of the patients presented a target AUC between 80 and 125 mg l^{-1} h and 61% were lower than 80 mg l^{-1} h. After considering COCK and height, MCS showed that only 50% of the population could achieve the target AUC for the 375 and 400 mg dosages.

CONCLUSION

Even after taking into account COCK and height, for strains with an MIC $\leq$ 1 mg l^{-1}, MCS doses evidenced that peak and AUC pharmacodynamic targets could not be reached simultaneously in more than 45% of the ICU patient population. Combination therapy in addition to drug monitoring are required to manage efficacy and toxicity.

Introduction

Infection in critically ill patients requires rapid bactericidal therapy such as a combination of an aminoglycoside with another antibiotic, particularly to treat gram-negative infections. Aminoglycosides have a concentration-dependent bactericidal effect and many reports have shown the efficacy of a once daily dosing (ODD) regimen [1–4]. Several pharmacodynamic indices have been shown to be related to aminoglycoside effectiveness: notably the ratio of the peak concentration (C_{max}) to MIC [5–7] and the area under the time–concentration curve (AUC) above the minimum inhibitory concentration (MIC) [8–10]. The ratio of C_{max} to MIC is easy to use in clinical practice. A value between 4.5 and 10 is predictive of clinical success in more than 85% of cases [11]. When C_{max} is at least 10 times the MIC of the causative gram-negative pathogen, the optimum antibacterial activity is achieved [12] and the emergence of aminoglycoside-resistant pathogens may be prevented [13]. Others have said that a target area under the aminoglycoside serum concentration–time curve (AUC) is more appropriate to evaluate efficiency and toxicity [10, 14] together [8]. They suggest achieving a tobramycin AUC between 80 and 125 mg l^{-1} h [9].

Data from animal models and clinical trials suggest that once-a-day regimens are as effective as conventional dosing for the treatment of gram-negative infections, but reduce the oto- and nephrotoxicity associated with aminoglycoside therapy [15]. To obtain a lower incidence of toxicity, a variety of authors have recommended or implied that trough concentrations of less than 1 mg l^{-1} are acceptable when using once daily dosing [16–18].

Several studies and meta-analyses have documented the efficacy of once daily dosing regimens compared with conventional administration [4, 19, 20]. However, few studies have analyzed the use of a once daily dosage regimen of tobramycin (TOB) in intensive care unit patients [21–24] or in burn patients [25]. In intensive care units, tobramycin is essentially used combined with beta-lactams, for the treatment of *Pseudomonas aeruginosa* infections [22].

Aminoglycoside disposition is highly variable in critically ill patients [22, 26–29]. Decreases in renal function can alter the clearance of aminoglycosides with an increased risk of toxicity [30]. On the other hand, an increased volume of distribution may result in a decreased peak concentration and a longer half-life [23]. During population pharmacokinetic studies, variability was explained by creatinine clearance for tobramycin clearance [24, 31] and weight for the volume of distribution [31]. To ensure efficiency, the target concentrations must be reached as soon as possible to avoid the persistence of gram-negative organisms [32, 33]. Therefore, high doses of 5 to 7 mg kg^{-1} of gentamicin or tobramycin associated with therapeutic drug monitoring are recommended by some authors [8, 22, 24].

The purpose of our study was to evaluate the pharmacokinetic parameters of once daily tobramycin regimens in ICU patients by a population approach, to explore the covariates of the pharmacokinetic parameters and to simulate tobramycin dosage regimens in these specific patients.

Methods

Patients

This retrospective study involved 49 adult patients, hospitalized in the ICU of the Toulouse-Rangueil University Hospital between October 2005 and December 2007, and treated for nosocomial infections by TOB associated with a beta-lactam antibiotic.

Patients were characterized by the usual severity indices in this pathology including simplified acute physiology scores (SAPS) I and II. The patients presenting a proven infection with gram-negative organisms sensitive to this aminoglycoside were included. All patients were haemodynamically stable. Pregnancy, age less than 15 years, drug allergies or intolerance to aminoglycosides, oligo-anuric renal failure and cochlear problems were considered contraindications to TOB administration.

The study was performed according to the declaration of Helsinki. Concentration data are presented anonymously in accordance with ethical considerations. The institutional review board of the hospital gave its approval because there was no change to the current clinical practice (TOB monitoring was part of the medical routine).

Clinical data were collected: age, sex, total bodyweight (TBW), ideal bodyweight (IDW) [34], height and reason for admission.

Administration and dosage of antibiotics

TOB was administered by intravenous infusion over 30 min at an initial daily dose of 5 mg kg^{-1} for 3 to 5 days. The associated treatment was ceftazidime or imipenem according to the strain susceptibility. For practical reasons, the therapeutic objective was defined as a TOB C_{max} between eight and ten times the MIC [35–38]. After the first administration, if necessary, the dosage regimen was empirically adapted according to the C_{max} result.

Biological evaluation

Various standard biological parameters were measured such as blood urea nitrogen (BUN) and creatinine. At the same time, creatinine clearance ($\mathbf{CL_{Cr}}$) was estimated with the Cockcroft [39] and Robert [40] formulae.

Tobramycin assay

The blood samples for assay were collected in dry 5 ml tubes. C_{max} was measured 30 min after the end of the infusion, i.e. 60 min after the beginning of the administration. C_{min} was measured prior to the following dose. When the C_{min} target (less or equal to 1 mg l^{-1} [24, 41] was

Table 1
Characteristics of the ICU patients in the model and qualification groups

	Group 1 model (n = 32)	Group 2 qualification (n = 17)	Total (n = 49)	P
Quantitative variables	Mean ± SD	Mean ± SD	Mean ± SD	
Age (years)	62.5 ± 15.3	58.6 ± 18.7	61.1 ± 16.5	NS
Body weight (kg)	77.5 ± 18.8	80.9 ± 19.4	78.7 ± 18.9	NS
Ideal body weight (kg)	71.7 ± 11.6	70.1 ± 8.5	71.1 ± 10.6	NS
Height (cm)	173 ± 10	172 ± 7	172 ± 9	NS
SAPS I	15 ± 3	15 ± 4	15 ± 4	NS
SAPS II	56 ± 15	55 ± 14	56 ± 14	NS
Serum creatinine (μmol l^{-1})	81.3 ± 30.4	89.8 ± 48.0	84.2 ± 37.2	NS
Cockcroft creatinine clearance (ml min^{-1})	106 ± 53	111 ± 60	108 ± 55	NS
Robert creatinine clearance (ml min^{-1})	75 ± 29	74 ± 32	75 ± 29	NS
BUN (mmol l^{-1})	10.4 ± 5.7	10.6 ± 7.2	10.5 ± 6.2	NS
Qualitative variables				
Sex (M/F)	27/5	13/4	40/9	NS
Incoming for poly-trauma	14	6	20	NS
Incoming for post-surgical	4	3	7	NS
Incoming for medical reason	14	8	22	NS

not achieved, new blood samples were drawn until re-injection.

Blood samples were immediately sent to the pharmacokinetics laboratory, centrifuged at 3000 rev min^{-1} at +4°C, and the serum concentrations were determined using the commercialized PETINIA method (Particle Enhanced Turbinometric Inhibition Immunoassay, Dade-Berhing-Siemens) on the RXL automate. The limit of quantification (LQ) was 0.3 mg l^{-1}, the precision was 7.47% and the accuracy 7.63%.

Statistical analysis

At the end of the study, an a *posteriori* randomization was carried out with 2/3 of the patients (group 1: 32 patients, 182 tobramycin concentrations greater or equal to the analytical quantification limit) for the model building and with 1/3 of the patients (group 2: 17 patients, 95 measurable tobramycin concentrations) for the qualification of the model.

The quantitative variables of the two groups presented in Table 1 were compared by using Student's *t*-test and the qualitative variables by the Chi^2 test.

Pharmacokinetic model building

The population pharmacokinetic analysis was carried out using NONMEM V [42] and Visual-NM V (RDPP, Montpellier, france, 1998) computer programs.

The first group of 32 patients was used to model the pharmacokinetics of tobramycin. A one- *versus* a two-compartment model was evaluated to describe the pharmacokinetics using the first order conditional estimation (FOCE) method with interaction. Proportional and exponential error models were evaluated to describe the inter-individual variability. The pharmaco-statistical model was fitted to the data to obtain the population parameters (mean and variance of each parameter), in terms of total body clearance in l h^{-1}, and the central and peripheral volumes of distribution in l. Individual pharmacokinetic parameters were obtained by using the Bayesian maximum a *posteriori* estimator.

For each individual pharmacokinetic parameter calculated by using the initial model, a multivariate analysis followed by a stepwise regression using Statview, led us to retain only statistically significant relevant covariates. Their influence was then examined in the structural model with a 0.05 level of significance, corresponding to a decrease in the objective function higher or equal to 3.84. The resulting pharmaco-statistical intermediate model was refined by independently deleting each covariate with 0.001 as the level of significance.

Qualification

The second group of 17 patients was used to qualify the constructed model.

The predictive performance of our intermediate model was evaluated by the generation of 1000 NONMEM Monte Carlo simulated concentrations sets from the qualification population. Then normalized distribution prediction error (npde) was evaluated by using R and the ndpe package [43].

Final model

The two populations were mixed after the qualification process. Population and individual parameters were then re-evaluated for the whole population and qualified by the npde calculations.

Simulation and dosage regimen propositions

The final model was used to perform by using NONMEM 1000 Monte carlo simulations as a function of the pair of significant covariates, patient height and Cockcroft

clearance. Tobramycin concentrations were simulated for a dosage regimen ranging from 300 to 550 mg with steps of 25 mg, for an ICU patient with median characteristics (height = 172 cm and Cockcroft clearance = 94 ml min^{-1}).

After simulation, we determined the percentiles of our simulated population which reach each of the following goals:

1 Pharmacodynamically, the efficiency of tobramycin requires a peak concentration 10-fold higher than the MIC of the strain chosen at 1 mg l^{-1} because in our population 70% of the isolated strains presented a MIC lower than 1 mg l^{-1}. The time of the peak was defined 30 min after the end of the infusion according to the aminoglycoside therapeutic drug monitoring (TDM) recommendations [9].
2 On the other hand, the toxicity of tobramycin means it cannot be re-injected before a trough concentration equal or less to 1 mg l^{-1} [16, 24, 41, 44] is attained.
3 AUC represents the total exposure to a drug and is relevant for both efficiency [8] and toxicity [10]. The usual goal corresponds to an AUC of 100 mg l h^{-1}; a variability range of 80–125% used by regulatory agencies as the bioequivalence criteria was adopted empirically [9].

We also determined the time (step of 1 h) required for 95% of the population to reach a concentration lower or equal to 1 mg l^{-1}.

Results

Patients

Forty-nine patients (nine females and 40 males) were included in the study and their characteristics are shown in Table 1.

They were hospitalized in the intensive care unit following a poly-trauma (n = 20), post-operative complications (n = 7) or for medical reasons generally dependent on a respiratory disease (n = 22). Their SAPS I was equal to 15 ± 4 and the SAPS II to 56 ± 14. The administration of antibiotics was carried out on average 18 ± 13 days after admission. All the patients were mechanically ventilated. Figure 1 shows the individual concentrations *vs.* time normalized to one administration. Figure 1A shows the results over the first 4 h and Figure 1B over the whole administration period on a semilogarithmic scale. These graphs showed that, in clinical practice, after one administration, blood sampling occurred at various times.

Basic pharmaco-statistical model

The pharmaco-statistical model was chosen as a two-compartment open model with an exponential inter-individual error model. We selected the best model on the lowest objective function and according to the distribution of the residuals (RES = observed concentrations – predicted concentrations) and of the weighted residuals (WRES = residuals/ variance) compared with the predicted concentrations.

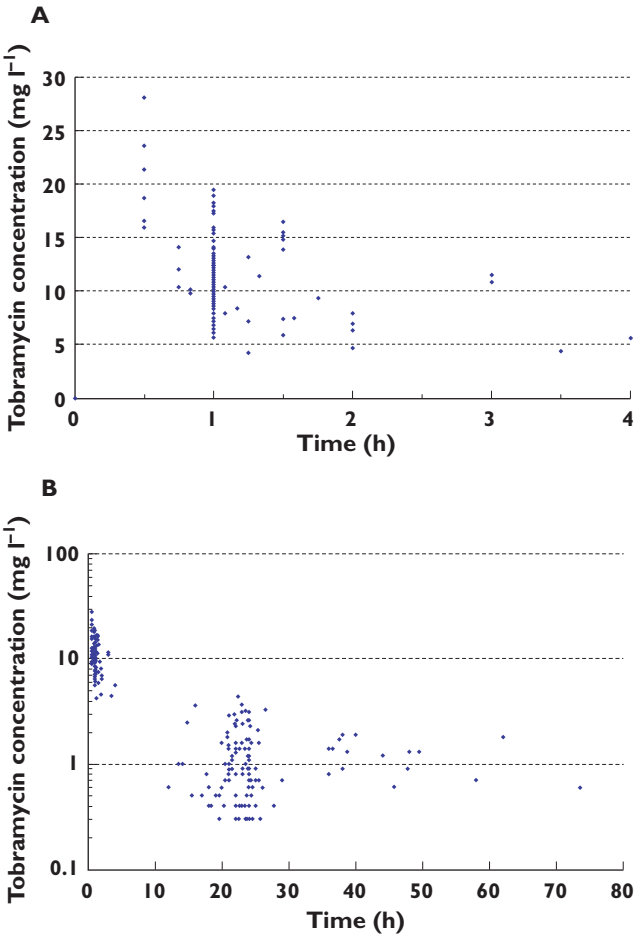

Figure 1

Serum tobramycin concentrations *vs.* time in 49 ICU patients on the first 4 h after administration (A) and on a semi-logarithmic scale over the whole administration period (B)

Our basic model was characterized by the following equation: C_{Pred} = 0.906 × C_{Obs} + 1.360 with an objective function equal to 381. As shown in Table 2, clearance was 3.4 l h^{-1} (range 2.75–4.05), intercompartmental clearance was 4.74 l h^{-1}, the volume of distribution of the central compartment was 26 l (range 23.4–28.6) and that of the peripheral compartment was 40 l (range 26.3–53.7). Since the variability of the inter-compartmental clearance was very low, the variance was fixed to zero.

Influence of covariates

After the stepwise regression process, we only retained statistically significant covariates. For tobramycin clearance, these were reason for admission, IBW, height, BUN, creatinine, Cockcroft and Robert creatinine clearance. After the independent deletion step, Cockcroft creatinine clear-

Table 2

Objective function, pharmacokinetic parameters, thetas, inter-individual omegas and intra-individual sigma (precision of the parameter = CV%) in the basic, intermediate and final model

		Basic model (n = 32)	Intermediate model (n = 32)	Final model (n = 49)
Objective function		381*	335*	449*
Coefficients				
CL (l h^{-1})	Theta 1	3.40 (10%)	3.95 (7%)	3.83 (6%)
	Theta 2	–	0.014 (47%)	0.020 (24%)
	Theta 3	–	0.062 (36%)	0.052 (32%)
V_1 (l)	Theta 4	26.00 (5%)	25.90 (5%)	25.50 (4%)
Q (l h^{-1})	Theta 5	4.74 (45%)	4.74 (45%)	4.74 (46%)
V_2 (l)	Theta 6	40.00 (17%)	31.60 (12%)	30.60 (13%)
Inter-individual variability				
CL (l h^{-1})	Omega 1	0.307 (28%)	0.105 (24%)	0.095 (19%)
V_1 (l)	Omega 2	0.046 (54%)	0.043 (45%)	0.045 (35%)
Q (l h^{-1})	Omega 3	Fixed	Fixed	Fixed
V_2 (l)	Omega 4	0.075 (287%)	Fixed	Fixed
Intra-individual variability				
Sigma 1		0.051 (22%)	0.056 (18%)	0.055 (15%)

Intermediate and final model are described by the following equations:
TVCL = THETA(1) + (THETA(2) × (COCK-94)) + (THETA(3) × (HEIG-172))
TVV_1 = THETA(4)
TVQ = THETA(5)
TVV_2 = THETA(6)
CL = TVCL × EXP(ETA(1)); V_1 = TVV_1 × EXP(ETA(2))
Q = TVQ × EXP(ETA(3)) V_2 = TVV_2 × EXP(ETA(4))
where THETA = mean pharmacokinetic parameters estimations, ETA = intra-individual variabilities, Omega = variance representing the inter-individual variability; Sigma: Variance of the residual error, COCK = Cockcroft creatinine clearance, HEIG = height. TVCL, typical value of tobramycin clearance in the studied population, TVV_1, typical value of the distribution volume of the central compartment, TVQ, typical value of the inter-compartmental clearance and TVV_2, typical value of the distribution volume of the peripheral compartment. *the objective functions of the basic and intermediate model could be compared. The third value corresponding to the final model has been calculated on a full dataset and cannot therefore be compared with the first two.

ance and height were finally included in the tobramycin clearance equation. These processes reduced the objective function from 380.793 to 346.839 for Cockcroft creatinine clearance alone and to 335.779 for Cockcroft creatinine clearance and height combined.

No covariate was evidenced as significant for the two volumes of distribution and the intercompartmental clearance. The equations of the model are given in Table 2.

The introduction of Cockcroft clearance alone reduced the variability of CL_{TOB} from 55% to 35%, and that of height to 39%. The introduction of both covariates allowed CL_{TOB} variability to fall to 29%.

Qualification

The npde qualification results did not show any evidence of bias for the prediction and the normality assumption was not rejected. The expected values were mean = 0, variance = 1, skewness = 0 and kurtosis = 0. The results of our qualification process were mean = –0.004258, variance = 0.9412, skewness = 0.1241 and kurtosis = 0.1124.

Final model

After the qualification process, all the data were pooled and the final model was determined in the 49 patients. The predicted *vs.* observed concentrations are shown in Figure 2 for the whole ICU population. This shows that our final model was characterized by the following equation: $C_{Pred} = 0.906 \times C_{Obs} + 1.01$. Figure 3 represents the npde of the total population. The graph of the npde function of the predicted concentrations showed that the lower the concentrations, the higher the variability. The results were mean = –0.04114, variance = 0.9532, skewness = 0.1564,and kurtosis = 0.05607. These results did not show any bias for the prediction and the normality assumption was not rejected.

Clearance was 4.8 ± 1.9 l h^{-1} (range 1.22–8.95) and the volume of distribution of the central compartment was 24.7 ± 3.7 l (range 17.34–32.83). That of the peripheral compartment was equal to 30.6 l and its inter-individual variability was fixed. The inter-compartmental clearance was 4.74 l h^{-1} without inter-individual variability. The terminal half-life based on *post hoc* estimates was 9.9 ± 5.6 h (range 3.9–29.9).

In the tested population, AUC was 86.1 ± 35.6 mg l^{-1} h. Thirty patients (61%) presented with an AUC lower than 80 mg l^{-1} h, five patients (10%) an AUC higher than 125 mg l^{-1} h and only 14 patients (29%) achieved the target AUC.

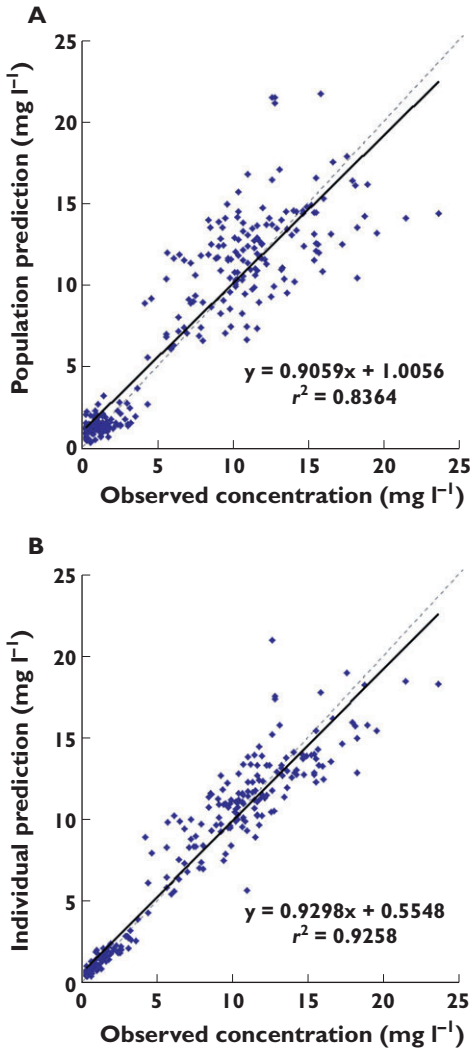

Figure 2

Scatter plot of predicted and individual predicted tobramycin concentrations *vs.* observed concentration in the total ICU population ($n = 49$). The grey dashed line corresponds to the identity line

Simulation and propositions for dosage regimens

Figure 4 represents the probabilities of achieving the efficacy and non toxicity targets of various tobramycin dosages used to treat infections due to a pathogen with an MIC less or equal to 1 mg l^{-1}. For a patient with typical covariate values, the peak target could be reached at 90% with a 525 mg dose. However, as shown in Table 3, the 24 h concentration is 1.68 $\pm$ 0.85 mg l^{-1} and the non toxicity will be unsure after 57 h in 95% of the population. For this dosage, only 35% of the population will have their AUC included in the 80–125 mg l^{-1} h range.

In a patient with typical covariate values, to maximize simultaneously peak and AUC, the best compromise would be a 325 mg dosage. The peak and AUC targets could not be reached in more than 45% of the simulated population and re-injection would be at 44 h.

Discussion

For more than 20 years, aminoglycosides have been given once daily to ICU patients but the disposition of tobramycin is poorly described under these conditions [21, 22, 24]. Several population PK models for aminoglycosides have been developed [45] but there was no model to assist a target concentration and AUC value intervention in a population of ICU patients. Some studies have reported the disposition of gentamicin and tobramycin but the data are difficult to interpret because they are pooled for both antibiotics [21, 22, 31]. The study reported by Peris-Marti *et al*. evaluated the pharmacodynamic effectiveness of a 4 mg kg^{-1} TOB dose in 51 adult ICU patients with creatinine clearances over 60 ml min^{-1}. These authors only fitted peak and trough tobramycin concentrations by using a one compartment model and a maximum *a posteriori* Bayesian analysis with the PKS program [24]. Rea *et al.* reported a NONMEM monocompartmental analysis in ICU patients for tobramycin and gentamycin. Glomerular filtration rate and standardized bodyweight were identified as covariates for clearance and distribution volume, respectively. The model was validated and a pharmacodynamic approach was developed based only on peak concentration [31].

The aim of our study was to construct and qualify a NONMEM pharmacokinetic model for once daily dosing of tobramycin in ICU patients; and then to propose dosage regimens for this specific population based on pharmacokinetic and pharmacodynamic targets.

We developed a population pharmacokinetic model by using a bi-compartmental approach with a proportional error model. The bi-compartmental disposition is well described for aminoglycosides [9, 45, 46] even if several cases were reported with a mono-compartmental model [21–23, 31]. When the sampling scheme allows a multi-compartmental analysis, this is appropriate, to characterize optimally the elimination as well as deep distribution phases [9, 47].

The interest in the population approach lies in the covariates which allow a reduction in the intra- and inter-individual variability [42, 48]. Height and creatinine clearance (CL_{CR}) estimated by the Cockcroft formula were identified as significant. CL_{CR} has already been found to be relevant to explain the variability of aminoglycoside clearance [22, 31, 45, 46, 49, 50]. It has been stated that TOB is mainly eliminated as an active form essentially by glomerular filtration: 85 to 93% of the administered dose is excreted in an unchanged form [51]. However, in 19 critically ill trauma patients Barletta *et al.* showed using 53 concentrations that weight, age or serum creatinine did not significantly explain the variability in aminoglycoside clearance [21].

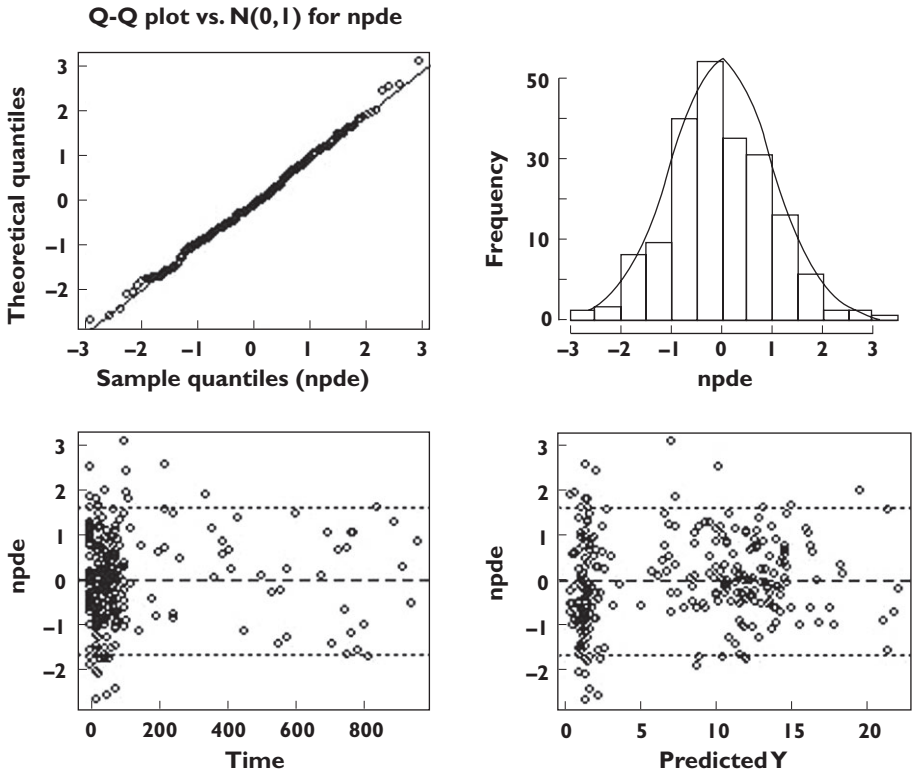

Figure 3

Model evaluation for the total population: Quantile-quantile plot of npde *vs.* the expected standard normalized distribution (upper left). Histogram of npde with the density of the standard normal distribution overlayed (upper right). Scatterplot of npde *vs.* observed time (lower left) and npde *vs.* predicted Y (concentration) (lower right)

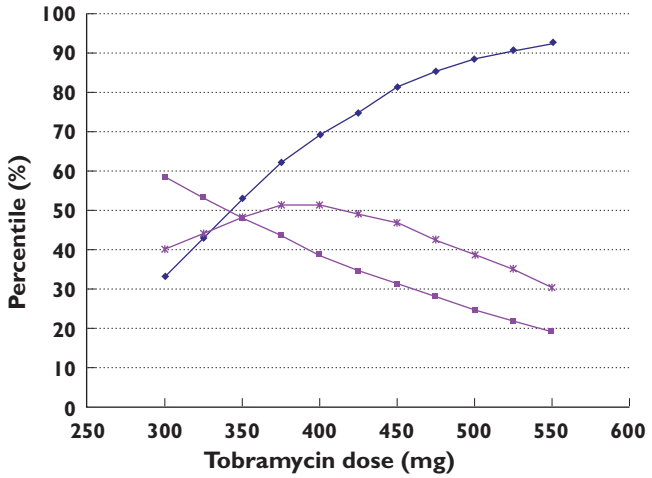

Figure 4

Probabilities of achieving the efficacy and non toxicity targets of various tobramycin doses used to treat infections due to a pathogen with an MIC less or equal to 1 mg l^{-1}. The calculations are based on 1000 Monte Carlo simulations for patient with typical covariate values (height 172 cm and Cockcroft clearance 94 ml min^{-1}). Pharmacodynamic targets were defined as a trough concentration less than 1 mg l^{-1}, a peak higher than 10 mg l^{-1} and an AUC between 80 and 125 mg l^{-1} h. Peak >10 mg L^{-1} (—◆—); Trough at 24 h <1 mg L^{-1} (—■—); 80 < AUC < 125 mg L^{-1} h (—✳—)

Table 3

Simulated peaks, 24 h concentrations and total AUC after 1000 Monte Carlo simulations of various tobramycin dosage regimens for a patient with typical covariate values (height 172 cm and Cockcroft clearance 94 ml min^{-1}). The time (h) corresponding to 95% of the simulations achieving the trough target concentration of less than 1 mg l^{-1} is also reported

Dose (mg)	Peak (mg l^{-1}) Mean ± SD	$C_{24\,h}$ (mg l^{-1}) Mean ± SD	AUC (mg l^{-1} h) Mean ± SD	Time 95% (h)
300	9.01 ± 2.64	0.96 ± 0.48	82 ± 27	42
325	9.76 ± 2.86	1.04 ± 0.52	89 ± 29	44
350	10.51 ± 3.08	1.12 ± 0.56	96 ± 31	46
375	11.26 ± 3.30	1.20 ± 0.60	103 ± 33	48
400	12.01 ± 3.52	1.28 ± 0.64	109 ± 35	50
425	12.76 ± 3.75	1.36 ± 0.68	116 ± 38	52
450	13.51 ± 3.97	1.44 ± 0.73	123 ± 40	54
475	14.26 ± 4.19	1.52 ± 0.77	130 ± 42	56
500	15.01 ± 4.41	1.60 ± 0.81	137 ± 44	57
525	15.77 ± 4.63	1.68 ± 0.85	144 ± 46	57
550	16.52 ± 4.85	1.76 ± 0.89	150 ± 49	57

The influence of height as a factor of variability of CL_{TOB} has not been reported in the literature. In fact, height is highly related to bodyweight but in our study its relationship with CL_{TOB} was stronger than that of TBW and IBW. In an

ICU patient weight is a poor parameter due to oedema which could be very large and introduce a bias. Even if weight has been used for dosage determination for a long time, it is not a sufficient parameter [52] since 'body composition' may be different despite two patients having the same total weight. In our study, elimination was also function of the Cockcroft clearance which already includes TBW.

In healthy subjects, tobramycin (TOB) exhibits low protein binding (<10%), a total body clearance of 6 to 7.2 l h^{-1}, and a renal clearance of 4.8 to 5.4 l h^{-1}. The normal elimination half-life is 2 h [46, 51].. In our patients tobramycin clearance was 4.8 $\pm$ 1.9 l h^{-1} corresponding with that reported by Matthews *et al.* [45] in non ICU patients. In ICU patients, Peris-Marti *et al*. [24] and Rea *et al*. [31] presented lower glomerular filtration rates corresponding to lower aminoglycoside clearances (0.0415 $\pm$ 0.004 ml min^{-1} kg^{-1} and 3.14 l h^{-1}, respectively). Barletta *et al*. reported in 19 patients a higher total body clearance of 5.47 l h^{-1} [21]. Bujik *et al*. found approximatively the same tobramycin clearance (85 $\pm$ 40 ml min^{-1}) in ICU patients with creatinine clearances higher than 60 ml min^{-1} [22]. These two studies used sparse sampling schemes and a simplified monocompartment model leading to an artefact in the estimation of the clearance. Our Bayesian approach showed a clear and significant relationship between the tobramycin clearance and the estimated creatinine clearance, which underlines the importance of the renal function shown in other studies with other types of pathology and/or drugs [25, 45, 46, 50, 53–55].

In our study the total volume of distribution was considerably increased, higher than 50 l. An increased volume of distribution of aminoglycosides in critically ill patients is well-known [26, 29]. Based on the expected poor ability to cross cell membranes the apparent volume of distribution of aminoglycosides is expected to be close to the extracellular fluid volume. Aminoglycosides are known to be taken up into certain tissues by active transport mechanisms, which may account for some of the additional apparent volume beyond that of the extra cellular fluid [45]. Many other factors are likely to increase this parameter [56]: serious septic state [22], unstable haemodynamic state, mechanical ventilation [57, 58], neutropenia, severe burns [59], renal, hepatic and cardiac failure, etc. Moreover, the volume of distribution is influenced by the severity of the illness [60] and by infection and inflammation which are potential reasons for a high extent of tissue penetration [10]. Our patients were mechanically ventilated, haemodynamically stable but presented with serious septic states and required antibiotic treatment. Consequent to this increased volume of distribution, the peak concentration was lower than expected in these critically ill patients and possibly not effective.

Since only 29% of our population achieved the target AUCs, we simulated dosage regimens constructed to achieve a trough concentration less than 1 mg l^{-1}, a peak higher than 10 mg l^{-1} and an AUC between 80 and 125 mg l^{-1} h, for bacterial strains having a MIC $\leq$ 1 mg l^{-1} and for an ICU patient with typical covariate values (height 172 cm and Cockcroft clearance 94 ml min^{-1}). In this case, the mean peak target could be reached for a dose higher than 325 mg even if only 50% of the 1000 simulations reach the goal. The 24 h concentrations presented a high variability. A mean 24 h concentration lower than 1 mg l^{-1} could only be reached for a 300 mg dose. Out of these 1000 simulated patients less than 60% present an individual value lower than 1 mg l^{-1}.

The individual target AUC could only be reached in these conditions in 50% of the cases for the 375 and 400 mg doses. Figure 4 clearly showsthat all the targets could not be reached simultaneously. For some authors high AUC could correspond to aminoglycoside toxicity [10] but achieving a larger AUC would be preferable to maximize killing and prevent resistance. In this population, to ensure a lower toxicity, an extension of the dosing interval was required and it could be found in the summary of product's characteristics. The trough concentration must be evaluated to decide the re-injection time. If the dosing interval for the aminoglycoside needs to be very long, addition of a carbapenem (or other beta-lactam) as done in our study (imipenem or ceftazidime) seems a viable approach. This is important because treatment of patients with aminoglycosides may be further complicated by clinical failures due to small colony variants.

In the studied population, 70% of the bacterial strains presented MICs lower than 1 mg l^{-1} and the highest MICs were equal to 2 mg l^{-1} and corresponded to 12% of the strains. In patients with an infectious disease caused by a bacterial strain having an MIC higher than 1 mg l^{-1}, very high dosages are required. The safety of these doses has not been established [24, 61] and, in our opinion, there are still doubts concerning a once daily dosing regimen in such a situation.

In conclusion, this study highlights the peculiarities of tobramycin pharmacokinetics in critically ill patients. Cockcroft creatinine clearance and height significantly influenced TOB disposition and partially explained its large pharmacokinetic inter-individual variability.

The volume of distribution of tobramycin is considerably increased in ICU patients exposing them to the risk of insufficient peak concentrations necessary to exceed the MIC of many pathogens.

Our study showed that the tobramycin peak and AUC pharmacodynamic targets could not be reached simultaneously in more than 45% of patients in the ICU population. In clinical practice, combination therapy in addition to drug monitoring leads the physician to choose the 'least worse' dosage regimen. In all cases, peak and trough concentrations have to be monitored very carefully.

Competing interests

There are no competing interests to declare.

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