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Bicompartmental kinetics of tobramycin analysed with a wide range of covariates

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Abstract

The pharmacokinetics of tobramycin was studied in adult patients ($N = 151$) admitted either for initial suspicion of Gram-negative infection or for prophylaxis. In addition to age, weight, height and creatinine clearance (CrCL), a range of other covariates were also analysed, including type of pathology, co-medication, fever, sex and ethnicity (Basque or not). All patients received 100 mg tobramycin every 8 h and samples were collected at three time points after the first dose and at two time points after the fourth dose and assayed with a fluorescence polarisation immunoassay. The population mixed effects bicompartmental parameters were obtained from 725 concentration measurements using NONMEM, FOCE method, and were: systemic clearance, CL = 6.03 L/h (between-subject coefficient of variation (CV) %, 29.4%); volume of distribution, $V = 15.04$ L (7.3%); and intercompartmental constants, $k_{12} = 0.192\ h^{-1}$ (56%) and $k_{21} = 0.55\ h^{-1}$ (no CV% determined). Covariate modelling was performed within NONMEM. Two alternative significant covariate models (Models 1 and 2) are proposed, with functions of CrCL and/or sex (Model 2). However, for clinical purposes, differentiation by sex is insignificant. Model 1 is for $CL = 3.1 + 0.05 \cdot CrCL$ L/h (17.3%); $V = 14.6$ L (12%); $k_{12} = 0.224\ h^{-1}$ (63%) and $k_{21} = 0.468\ h^{-1}$. Stochastic simulation was used to predict the expected concentration 95th percentiles after the recommended 7 mg/kg dose and for minimum inhibitory concentration (MIC) = 1 mg/L, as well as alternative once-daily dosing regimens for MIC = 2 mg/L. It is seen that once-daily high-dose tobramycin is an appropriate strategy with respect to pharmacodynamic indices, C_{peak}/MIC or AUC/MIC (where C_{peak} is the peak plasma concentration and AUC is the area under the concentration–time curve).

Keywords: Tobramycin; Population pharmacokinetics; NONMEM; Covariates; Monte Carlo; Pharmacodynamics

1. Introduction

The aminoglycosides represent an important class of antibiotic agents, used mainly in patients with severe infections caused by Gram-negative bacteria [1]. Aminoglycosides are polar cations, hence their pharmacokinetic (PK) properties are not ideal. They are not absorbed after oral dosing, have renal-dependent elimination and their volume of distribution is small, but they do bind to sensitive tissue, raising the risk of kidney toxicity and ototoxicity. Binding to serum protein is not problematic since it is less than 10% and is not considered clinically significant [2]. Specifically, tobramycin is distributed to most fluids in the body, including the peritoneal, synovial, pleural and pericardiac, but less so in bile, prostate and amniotic fluid, and negligibly in the central nervous system. Elimination is mainly via glomerular filtration through an unknown mechanism of active filtration [3].

Despite the potential for toxic effects and adverse PK properties, the aminoglycosides have not been phased out by the newer families of agents such as the quinolones, and their use is still increasing. In the USA alone, over 3 million doses

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are administered per year. Curiously, the search for improved agents, which is common for other families of antimicrobial agents, is not the case with the aminoglycosides. The wide use of aminoglycosides since the 1970s (after the introduction of the last semi-synthetic agents) revealed problems with toxicity and bacterial resistance, but it was also verified that the aminoglycoside molecule could not be modified to reduce its toxicity, or to improve its PKs, without reducing its antimicrobial activity. Therefore, research in the last years focuses on broadening the knowledge of aminoglycoside PKs and pharmacodynamics (PDs) and evaluating interpatient variability in order to apply new dosing strategies (e.g. once daily) for optimum therapy [4–6].

With regard to the variability in plasma concentration (C_p) after similar doses, there is consensus on the need to monitor C_p in prolonged treatment to keep the levels within a specific target range. The range depends on a PD that is not classical (i.e. relating potency (EC_{50}) and efficacy (E_{max}) with drug concentration C_p), but is based on minimum inhibitory concentration (MIC) as well as its ratio with the peak plasma concentration (C_{peak}) and the area under the concentration versus time curve (AUC) as PD indices (PDIs). However, the MIC itself depends on the targeted microorganism, which may complicate selection of the optimal dose. In general, the objective of treatment with aminoglycosides is to raise the C_{peak} by administering the maximum dose permitted before toxicity [7].

Tobramycin is an antimicrobial drug belonging to the concentration-dependent group of antimicrobials, therefore its in vivo effect is related to C_{peak} or the AUC. PDIs can be established with the ratio $C_{peak}/MIC \geq 10$ or $AUC/MIC \geq 100$ as valid bactericidal predictors or for reducing selection of resistant subpopulations [8]. Both C_{peak} and AUC can be explained and predicted by PK compartmental parameters such as the systemic clearance (CL) and volume of distribution (V), which are independent of dose. Nevertheless, the variability in the observed measures, and hence the difficulty to adjust follow-up doses, is linked to the variation of compartmental PK parameters among patients and populations.

There therefore exists concern regarding the appropriate dose for initiating treatment within a specific population or group of patients, particularly for short treatment cases where it is not necessary, or feasible, to monitor the concentrations; also, once a C_p has been measured, on how to adjust the next dose. Good knowledge of the PK parameters and their variability would help to optimise the following dose in a multidose strategy (i.e. every 8 h (q8h) for tobramycin) or even once-daily schemes, although knowledge of antibacterial PDI parameters is also required [9].

In the present study, unpublished data from a hospital project comparing monitoring methods for tobramycin are analysed using a population PK method (NONMEM). The samples were from hospitalised patients with different Gram-negative infections or from patients on prophylaxis. The observations are analysed with the objective of obtaining typical population PK parameters and their variabilities. Monte Carlo sampling techniques are used, based on these parameter distributions, to simulate the expected blood levels of tobramycin in the currently typical 7 mg/kg as well as alternative dosing strategies to reach the target AUC and PDI surrogates of bactericidal effect.

2. Materials and methods

2.1. Study design

The study covered 14 months in the Galdakao Public Hospital (Vizcaya, Spain), a service addressing a region of 260 000 inhabitants. The population sample incorporated adult patients under treatment with tobramycin for opportunistic Gram-negative infections, or patients under prophylaxis for colon surgery.

Inclusion criteria were age over 18 years at the time of admission, lack of any intolerance to aminoglycosides and normal renal function. Serum creatinine was to be less than 1.3 mg/dL for men and 1–2 mg/dL for women, which was increased in cases of obesity to 1.5 mg/dL for men and 1.4 mg/dL for women. The study was approved by the Committee for Clinical Trials of the hospital and written informed consent was obtained from all subjects related to the five blood samples for PK determination.

All patients were administered 100 mg tobramycin intravenously at a rate of 30 min q8h. The surgery prophylaxis patients were co-administered 500 mg of metronidazole. When other antibiotics were administered, those with known PK interaction with aminoglycosides were avoided, particularly carbenicillin, ticarcillin and piperacillin, although most interactions concern patients with renal dysfunction. Antibiotic administration in our group was performed at different times from intravenous tobramycin.

Seven samples were extracted from each patient from the contralateral arm from that of the infusion. Extraction times were 1 h (0.5 h after the end of infusion), 4 h, 8 h, 25 h and 32 h post dose. The blood samples were immediately separated into two vials each (to prevent loss) and centrifuged. Plasma was stored at $-70\,^{\circ}C$ to minimise inter-day analytical variability. Concentration levels of tobramycin were determined with fluorescence immunoassay analysis in a TDx system (Abbott Diagnostics, Irving, TX). The lower limit of detection for the assay was 0.18 mg/L.

2.2. Population PK analysis

The data set was analysed using a population PK method as implemented in the NONMEM package, version 1.1 (nonlinear mixed effects modelling; NONMEM Project Group, UCSF, San Francisco, CA) [10] on a Windows XP (Microsoft Corporation, Redmond, WA) PC system with a Pentium III processor (Intel Corporation, Santa Clara, CA). First, a base

(no covariate) population model was developed and then covariate modelling was undertaken.

The NONMEM-FO method was employed for initial data stream testing, but all subsequent (base and covariate) modelling was performed with the FOCE method. Both one and two disposition compartment PK descriptions were used to explain the observations with a parameterisation consisting of explicitly fitting parameters for systemic clearance (CL) and volume of distribution (V) and intercompartmental transfer rates, k_{12} and k_{21}. Exponential forms were used for the between-subject variability (BSV) statistical submodels (ETA variable). For the residual variance or within-subject variability (WSV), proportional or mixed (proportional and additive) models were tested. These methods have been described previously [11,12].

The software package includes a facility that estimates the empirical Bayes individual PK parameters for each patient in the analysis and for those parameters with an estimated variance parameter (ω^2), based on the distributions obtained in the population fitting run. Covariate modelling was performed with stepwise addition of the covariates versus the empirical Bayes parameters with a general additive model (GAM) procedure [13], included as a library in S-PLUS (Mathsoft, Inc., Seattle, WA). Exploration of colinearities among the covariates and PK parameters was performed graphically and also using SPSS (SPPS Inc., Chicago, IL). Once a model including the maximum number of covariates was created, it was introduced into NONMEM where the final covariate population model was created by backward elimination [14].

Model diagnosis for selection among alternative PK structures (monocompartmental or bicompartmental), statistical models for the BSV and WSV, as well as the covariate elimination followed the same criteria. These were: (a) the objective function change criterion (chi-square (χ^2) distributed). The objective function in least-squares-based algorithms is proportional to the sum of the weighted residuals, reflecting the deviation of the fitted model from the data. In covariate model backward reduction, a change in objective function of 10.83 was considered for one additional parameter (1 d.f.) and 13.82 for two parameters at the $\alpha = 0.001$ significance level in the upper tail of the χ^2; (b) the precision (standard error) for the parameters, and their reduction until significance (95% confidence interval ($CI_{95\%}$) not including zero), primarily for the structural PK parameters and then for the BSV variance (ω) estimates; (c) the distribution of weighted residuals versus predicted concentrations checking for a reduced homogeneous spread centred near 0; (d) reduction in the magnitude of the intra-individual residual. In covariate modelling steps, reduction in the magnitude of the BSV variance, corresponding to the model parameter, was also expected.

The process of covariate model creation within a population PK algorithm is lengthy and iterative [15], thus the scientist necessarily forms part of the decision loop. In this study, the choice of final models was also influenced by clinical significance in addition to the statistical criteria mentioned above.

2.3. Concentration range simulations

The base model population distributions were sampled by Monte Carlo (MC) methods and the bicompartmental kinetics reproduced for 10 000 virtual subjects at the currently proposed once-daily 7 mg/kg dose [16]. Thus, the expected mean and 95th percentile time course envelopes are estimated. The final model was sampled at the mechanistic extremes of the covariate distributions (e.g. upper and lower values of creatinine clearance (CrCL), or fast and slow eliminators) for the same dose. Since the current regimen of 7 mg/kg would mostly likely not achieve the putative PDI targets (C_{peak}/MIC $\geq$ 10 and AUC/MIC $\geq$ 100) for microorganisms with MIC > 1 mg/L (e.g. *Pseudomonas* with MIC = 2 mg/L), alternative once-daily dosing strategies were explored by simulation. This was done by varying (a) the dose to reach the desired AUC and (b) the infusion time to avoid excessive C_{peak} magnitudes. The specific aim was to improve the probability of achieving the desirable PDI.

3. Results

The demographic characteristics and pathologies of the patients employed as covariates in the population analysis are summarised in Table 1. At the end of the 14-month period, 151 patients had been included who required either treatment for Gram-negative or specific Gram-positive infections ($N = 111$) or surgery prophylaxis (in conjunction with metronidazole) ($N = 40$). Patients were classified as of Basque ethnicity or not, based on their genealogy. Of the non-prophylaxis patients, 18 (12%) had pneumonia, 13 (9%) sepsis (8 urological, 4 pulmonary, 1 abdominal), 40 (26%) acute pyelonephritis (the most common diagnosis), 16 (11%) fever of varying aetiology, 4 (3%) endocarditis and 20 patients (13%) had other pathologies.

Co-medication with metronidazole, another antibiotic or no co-medication were assigned as categories in a covariate for the PK analysis; 36 patients (24%) eventually received tobramycin alone. During the first 48 h of the clinical case study, the bacteria were identified in 49 cases. There were 35 patients with Gram-negative infections (23%) of *Escherichia coli*, the most frequent species, and 15 patients (10%) with staphylococcus or specific streptococcus. Eighty-three patients had another antibiotic associated with therapy. Eighty patients had fever above 37.5 °C and 33 (22%) above 38.5 °C; the latter occasion was included as a categorical covariate. CrCL was calculated according to a standard formula [17]. Lean body mass was also calculated for men and women separately.

Fig. 1 shows the observed concentrations for the 4 × q8h protocol applied in this case. The prediction from the typical base model is also overlaid. The 1 h post-dose C_{peak} varied

Table 1
Demographic and pathophysiological covariate summary of patients included in the pharmacokinetic study ($N = 151$) (the observed concentration extremes and area under the concentration–time curve (AUC) are also listed)

Characteristic		$N = 151$
Age (years)	Mean ± S.D.	51.3 ± 20.5
	Median	55
	Range	18–89
Weight (kg)	Mean ± S.D.	67.4 ± 12.5
	Median	66
	Range	43–130
Height (cm)	Mean ± S.D.	165.6 ± 9.8
	Median	166
	Range	145–189
SC (mg/dL)	Mean ± S.D.	0.92 ± 0.18
	Median	0.99
	Range	0.4–1.5
Sex[a]	Female	61 (40%)
	Male	90 (60%)
Basque ethnicity[a]	Yes	69 (46%)
	No	82 (54%)
Fever (>38.5 °C)[a]	Yes	33 (22%)
	No	118 (78%)
Co-medication[a]	None	36 (24%)
	Metronidazole	32 (21%)
	Other antibiotic	83 (55%)
Neoplasia[a]	No	122 (81%)
	Yes	29 (19%)
Pyelonephritis[a]	No	111 (74%)
	Yes	40 (26%)
Pneumonia[a]	No	133 (88%)
	Yes	18 (12%)
CrCL (mL/min)	Mean ± S.D.	62.8 ± 31.4
	Median	55.43
	Range	17.9–165.3
C_{peak} (at 1 h post dose) (mg/L)	Mean ± S.D.	4.75 ± 1.4
	Median	4.68
	Range	1.88–8.39
$AUC_{0–24}$ (mg h/L)	Mean ± S.D.	17.18 ± 5.0
	Median	15.91
	Range	8.6–36.92

SC, serum creatinine; CrCL, creatinine clearance; C_{peak}, peak plasma concentration.
[a] Number (and % rounded off to nearest integer).

across a four-fold range, and similarly for the observed AUC (Table 1), with 5% of all C_{peak} beyond the 95th percentile. The C_{peak}/MIC remained below the putative target of 10 (e.g. MIC = 1 mg/L for *E. coli* as well as the majority of the bacteria involved in our patient group) with this dosing strategy.

In preliminary analysis of the covariates, it was observed that weight was not correlated with any of the other covariates except for height and to a lesser extent with sex. Weight showed no relationship with C_{peak} or AUC. The strongest principal component was for CrCL. The empirical Bayes estimates for CL and V had a correlation of 0.58 owing to the non-optimal sampling design.

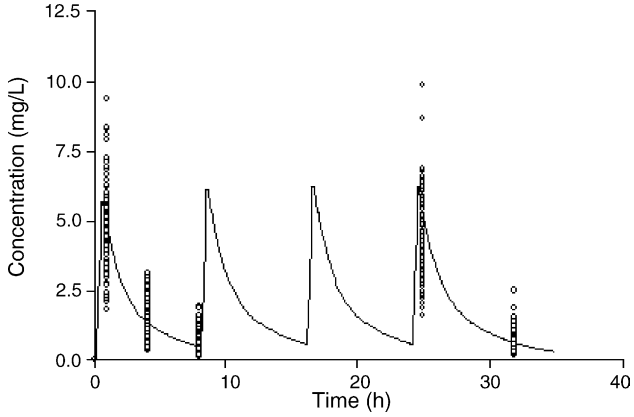

Fig. 1. Observed (open symbols) tobramycin concentrations in adult patients after four 100 mg doses every 8 h. The typical base population bicompartmental model prediction is also shown (solid line).

3.1. Population PK analysis

A bicompartmental disposition model best fit the observations, although the BSV variance for the k_{21} (return from the deep compartment) rate was not obtainable in this data set. The base bicompartmental population parameters from the index group are listed in Table 2. None of the $CI_{95\%}$ contained zero, and precision was high. The residual error estimate (σ) was nominal for PK problems (∼27%). The alpha and beta phase and central compartment half-lives are also listed in Table 2.

The distributions of all covariates were tested normal by the Kolmogorov–Smirnov test. In graphical representation,

Table 2
Base bicompartmental population (NONMEM, FOCE method) parameters for tobramycin in adults ($N = 151$)

	CL (L/h)	V (L)	k_{12} (h^{-1})	k_{21} (h^{-1})	σ (%)
Parameter estimate	6.03	15.1	0.192	0.451	26.67

	CL	V	k_{12}	k_{21}	σ
Precision of the estimate (%)[a]	2.9	8.5	43	26	6.3
Interpatient coefficient of variation (ω) (%)	29.4	7.3	55.8	–	–
Precision of the ω estimate (%)	10.9	11.3	40.4	–	

	k_{10} (h^{-1})	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	$t_{1/2\_k10}$ (h)
Calculated secondary parameter	0.40	0.84	3.2	1.7

Between-subject variability (BSV) and within-subject variability (WSV) are expressed as coefficients of variation per cent (BSV = 100·S.D./typical value). The elimination rate constant (k_{10} = CL/V), alpha and beta phase half-lives ($t_{1/2\alpha}$, $t_{1/2\beta}$) as well as the central compartment half-life ($t_{1/2\text{-}k10}$) are calculated and listed.
CL, systemic clearance; V, central volume of distribution; k_{12}, k_{21}, intercompartmental transfer rates; σ, intrapatient coefficient of variation.
[a] Obtained from standard error approximations of NONMEM as: precision = S.E./(typical value). A precision of over 51% is indicative of a 95% confidence interval that may include zero for the corresponding parameter estimate.

sex also appeared to differ with respect to demographic parameters but there were no significant differences obtained for the covariates versus sex. CrCL was a principal component for the continuous covariates (weight, height, age) and showed the strongest association with all covariates.

The GAM showed significant relations for CL with weight and CrCL. Also in the GAM, *V* was related to pyelonephritis, weight and CrCL. To test for significance of the categorical pathology covariates, CrCL was excluded from the combined empirical Bayes PK parameter covariate data set. Then, the relationships for CL were with weight and age, and for *V* with pyelonephritis, age, weight and height. Sex was also not a significant term for the S-PLUS or GAM models.

In covariate analysis with NONMEM, a full model was first created, guided by the preliminary covariate analysis and the GAM, including weight, age, CrCL and pyelonephritis (Model 1). An ad hoc model (Model 2) was also tried containing the categorical covariate sex on both CL and *V*, and CrCL on CL, at this point showing the best diagnostics and the lowest objective function. Backward elimination led to the final Model 1 (Table 3). Model 2 had significantly improved criteria ($P < 0.001$ by 2 d.f. χ^2 [=16.86]) compared with Model 1 and was considered as the final model and used for the simulations. The unexplained BSV in CL was reduced by 40% in Model 1 and 50% in Model 2. The BSV for *V* was increased in Model 1 compared with the base model, but reduced again in Model 2, similarly with its precision. The standard error (expressed as precision%) of the covariate coefficients was particularly satisfactory (near 10% of the estimated value). Since for clinical purposes the more complex Model 2 does not appear to offer appreciable improvement, Model 1 was the structure employed for further study via simulation.

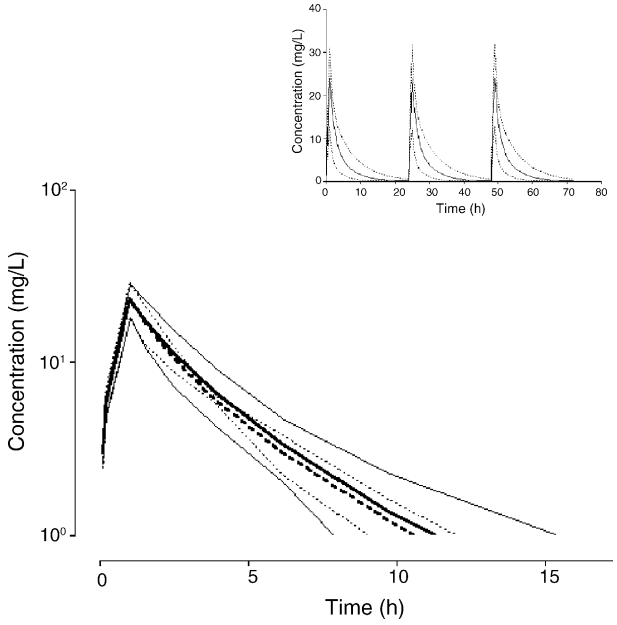

Fig. 2. Expected concentration time course ranges after 7 mg/kg (×67.4 kg) tobramycin from Monte Carlo (MC) simulation of 10 000 subjects sampled from the base (solid lines) and final Model 1 (dotted lines) population model distributions. The mean expected courses (bold) and 95th percentile ranges (thin lines) are shown. The final model span is conditional on the mean creatinine clearance (CrCL = 62.8 mL/min). The insert depicts a MC simulation of expected ranges after three consecutive tobramycin doses of 7 mg/kg every 24 h.

3.2. Concentration range simulations

The expected MC-simulated concentrations are depicted in Fig. 2 for a 7 mg/kg (×67.4 kg) tobramycin dose for 10 000 simulated subjects from the base and final (Model 1) models.

Table 3
Population covariate final models

Model 1	$CL = \Theta_1 + \Theta_5 CrCL$	L/h		$V = \Theta_2$ (L)	$k_{12} = \Theta_3$ (h^{-1})	$k_{21} = \Theta_4$ (h^{-1})
		Θ_1	Θ_5	Θ_2	Θ_3	Θ_4
Fixed effect estimate (precision%)[a]		3.07 (6%)	0.05 (7%)	14.6 (8%)	0.224 (35%)	0.468 (20%)
BSV coefficient of variation (precision%)	17.3% (6.8%)	–	–	12% (14%)	63% (41%)	Not estimated
WSV residual error σ (precision%)	26% (7%)					

Model 2: men[b]	$CL = \Theta_1 + \Theta_5 CrCL$	L/h Θ_1	Slope Θ_5	$V = \Theta_2$ (L) Θ_2	$k_{12} = \Theta_3$ (h^{-1}) Θ_3	$k_{21} = \Theta_4$ (h^{-1}) Θ_4
Fixed effect estimate (%)		3.5 (5%)	0.049 (6%)	15.5 (7%)	0.206 (35%)	0.442 (21%)

Model 2: women	$CL = \Theta_1\Theta_6 + \Theta_5 CrCL$	(—)[c] Θ_6	$V = \Theta_2\Theta_7$ Θ_7	$k_{12} = \Theta_3$ (h^{-1}) Θ_3	$k_{21} = \Theta_4$(h^{-1}) Θ_4
BSV coefficient of variation (ω)	15.4% (8.1%)	0.727 (15%)	0.89 (4%)	0.206 (35%)	0.442 (21%)
WSV residual error σ (precision%)	26% (7%)				

CL, systemic clearance; CrCL, creatinine clearance; *V*, central volume of distribution; k_{12}, k_{21}, intercompartmental transfer rates; BSV, between-subject variability; WSV, within-subject variability.

[a] For both fixed effect parameters and variance ω.

[b] The covariate sex was included for CL and *V* only. Typical CL and *V* for men would be $CL = 3.5 + 0.049 \times CrCL$ (L/h), $V = 15.5$ (L), and for women $CL = 2.5 + 0.049 \times CrCL$ (L/h), $V = 13.8$ (L).

[c] No units.

The base model (solid lines) shows larger spread, particularly regarding the overall exposure (AUC) rather than the peak concentrations. The conditional distribution from Model 1 (dotted lines) for the mean CrCL (62.8 mL/min) shows drastically reduced spread. The base model 95th percentile edges for AUC (or a PDI of AUC/MIC for MIC = 1 mg/L for *E. coli*) cover the range (mean) 47–108.5 (77) mg h/L, whilst the predictions conditional on the mean CrCL span 56–87 (71) mg h/L, reducing uncertainty by 50%, but not achieving the putative target PDI of AUC/MIC ≥ 100. The C_{peak} values were in the range 17–29 mg/L. This latter PDI was insensitive to the covariate model (for CL) owing to the larger dependence on V of C_{peak}. The insert shows the MC-simulated concentration–time courses after three once-daily 7 mg/kg tobramycin doses with the corresponding 95th percentile ranges. No accumulation is observed with this protocol at any level.

The distributions, conditional on sex and CrCL (Model 2), were sampled mechanistically for CrCL, i.e. for fast and slow drug eliminators. For each of the empirical range edges of CrCL, a typical CL was obtained for men and women and then MC simulation was used to produce the expected 95th percentiles. Fig. 3 shows a reduced plot as an example of the ranges observed overlaid on the base model mean and 95th percentiles (solid lines). The lower dashed line pair is the envelope of the expected concentration time courses (95th percentile span) for fast eliminators (CrCL = 165.3 mL/min), with a mean AUC of 40.5 mg h/L. The upper dotted line pair is the expected span for the reduced CrCL (17.9 mL/min) and mean AUC of 107.3 mg h/L. Although not depicted in Fig. 3, the expected concentrations for men and women had nearly overlapping time courses at both extremes, so application of separation by sex does not appear to be necessary for clinical purposes and particularly for few repeated doses. However, the deviations could become important in continued dosing and may prove useful in clinical trial simulations.

Once-daily dosing strategies, to increase the probability of achieving the PDI for MIC = 2 mg/L (e.g. *Pseudomonas*), were simulated by trial and error in 10 000 MC virtual subjects and the results are shown in Table 4. To avoid toxicity, the infusions were spread out in time, particularly for the fast

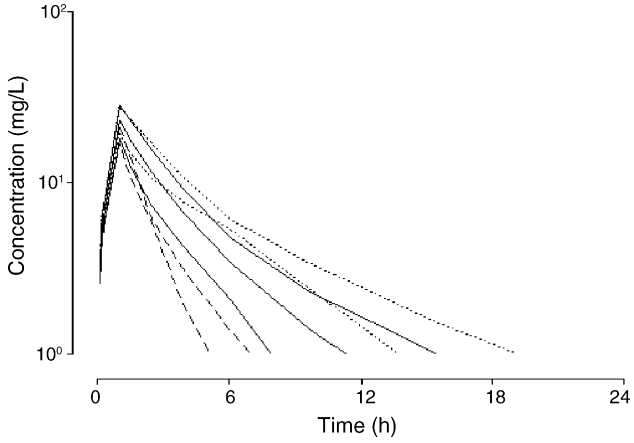

Fig. 3. Expected concentration time courses and 95th percentiles after 7 mg/kg (×67.4 kg) tobramycin by Monte Carlo (MC) simulation from conditional distributions for systemic clearance (CL) centred on mechanistic extremes of creatinine clearance (CrCL) from Model 1. The upper pair of dotted lines are 95th percentile envelopes for slow eliminators and the lower dashed lines are for the rapid eliminators. The solid lines are the mean and percentiles for the base marginal model. (The profiles for men and women are nearly coincident and are not depicted.)

eliminators, reaching or exceeding 4 h. Fig. 4 displays the 95th percentile expected concentration envelopes. Although the same C_{peak} magnitudes are reached, the half-lives are very different between the two clearance extremes and there is no overlap.

4. Discussion

The patients of the present study showed large variability in C_{peak} (1.88–8.39 ng/mL) and $AUC_{0–24}$ (9–37 mg h/L) after the initial uniform 100 mg dose. It is also interesting that most patients had concentrations below the putative PD C_{peak}/MIC target of 10 for a MIC of 1 mg/L. This has also been observed by other authors [18,19], particularly when the initial dosing is based on classical monocompartmental approaches with a fixed V_d (V_d = dose/C_{peak}) and not considering the PDs [20].

Tobramycin dosing is typically performed in a manner so that steady-state is not reached in either the every 8 h or every

Table 4
Once-daily dosing strategies used in simulations to target pharmacodynamic indices (PDIs) of C_{peak}/MIC > 10 and AUC/MIC > 100 for *Pseudomonas* (MIC = 2 mg/L) (systemic clearance (CL) is individualised by creatinine clearance (CrCL) at the covariate mean and extremes (max., mean, min.))

CL ~ CrCL (L/h)[a]	Daily dose (mg/kg) (×67.4 kg)	Infusion duration (h)[b]	Expected[c] $AUC_{0–x}$/MIC (range) (h)	Mean profile $AUC_{0–24}$ (mg h/L)
MIC = 2 mg/L				
11.33 (max.)[d]	34	≥4	99 (70–128)	202
5.84 (mean)	24	≥4	140 (94–183)	277
3.96 (min.)[d]	14	≥1	125 (88–162)	238

C_{peak}, peak plasma concentration; MIC, minimum inhibitory concentration; AUC, area under the concentration–time curve.
[a] Mechanistic extremes obtained from Model 1 and Table 1, CrCL values, e.g. CL_{max} = 3.07 + 0.05*165.3 = 11.33 L/h, etc.
[b] Adjusted to keep C_{peak}/MIC < 40.
[c] Calculated with the trapezoidal rule from the Monte Carlo simulated profiles. The time span x varied as seen in Fig. 4.
[d] Profiles shown in Fig. 4.

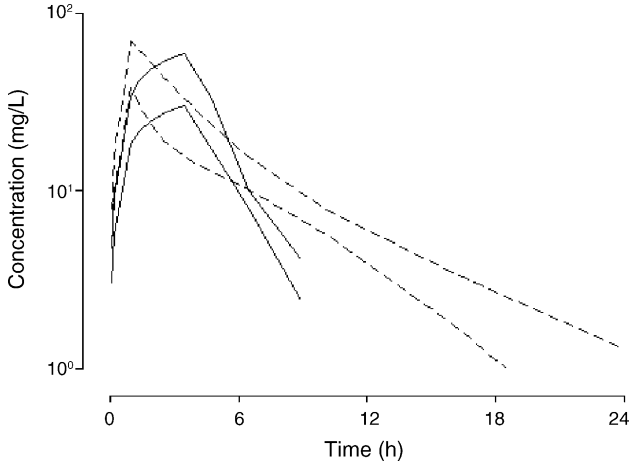

Fig. 4. Exploratory, increased complexity, strategies to increase the probability of targeting the AUC/MIC > 100 and C_{peak}/MIC > 10 pharmacodynamic indices for MIC = 2 mg/L (e.g. *Pseudomonas*). The expected 95th percentile envelopes are shown for rapid (solid lines) and slow (dotted lines) eliminators after Monte Carlo simulation of 10 000 patients. AUC, area under the concentration–time curve; MIC, minimum inhibitory concentration; C_{peak}, peak plasma concentration.

24 h strategies. Furthermore, since in many patient groups such as ours the first dose is repeated, determining a correct loading dose is crucial and this depends on V_d. On the other hand, in monitored patient groups, if re-adjustment is required, both V_d and CL (CL = dose/AUC) and its variability should be taken in consideration. It was considered that the variability in the next dose prediction could be reduced by correcting it with the CrCL. Nevertheless, better knowledge of these drugs has revealed that although they do not suffer metabolic alterations, they also have other, non-renal routes of elimination [21]. Therefore, adjustment of the dose using CL corrected by the individual CrCL reduces variability only slightly and in many cases C_p in the effective range is not achieved.

The complicated PKs of these compounds has to date not allowed the sources of variability to be resolved to the extent of permitting optimal dosing. The Bayesian feedback methods appear to give better results, but for many patients in prophylaxis and brief internal medicine treatment such as the patients in our group, there is no monitoring or feedback. Therefore, a method of selecting an appropriate dose since initiation is imperative to avoid adverse events or resistance creation. This dosing relies on a priori knowledge of the PK parameters of tobramycin. However, there are different PK representations in the literature for aminoglycosides, namely for monocompartmental [22–25] and bicompartmental [11,12,26,27] disposition models. Some authors suggest that the use of literature values for dose adjustment across different populations is not appropriate and that the PKs for each group should be determined separately, always the target PD [6]. However, population PK methods with covariate analyses including subgroups could help avoid extensive determinations.

Here, a bicompartmental population model for tobramycin best explained the concentration observations and resolved both the parameters and their distribution structure with high precision and fulfilling specific diagnostic tools. Multicompartmental PK analysis is appropriate, apart from statistical significance, to characterise optimally the elimination as well as deep distribution phases [28]. The parameters obtained here with the base model were similar to those from a heterogeneous group in the clinical setting [9,26]. The CL in those studies was related to CrCL via a linear relation with coefficients similar to the ones determined here with high precision.

To explain BSV, a number of categorical covariates, including pathologies, fever, co-medication and ethnicity, were analysed and two final models of possible clinical applicability were proposed. Model 1 had only CrCL on CL and was nested within Model 2 that had sex included for both CL and *V*. This covariate was also important for a population under netilmicin prophylaxis treatment [11]. *V* appears smaller in women with polar antibiotics, possibly in relation to distribution in extracellular fluid. In a recent population study, sex was also significantly related to the parameters [9]. The rest of the covariates did not lead to a significant improvement in the models, and including the large subgroups of pyelonephritis and pneumonia did not differ kinetically from the typical adult population. This result gives universality to our model for adult patients with nominal renal function and varying infections or in prophylaxis. Our models obviously do not cover neonates, cystic fibrosis (CF) disease, or the critically ill, where it is known that aminoglycosides show large variability in the PK parameters and are different from general patient groups [25,29]. Dosing in these groups is specific, either because of alteration in the PK parameters or in the PD target (e.g. MIC = 2 mg/L for pseudomonas in CF).

The results of the present study demonstrate that it is important to determine optimally the parameters both for the PK and PD indices (C_{peak}/MIC or AUC/MIC) to allow a priori dose prediction [30]. Knowing the C_{peak}/MIC for aminoglycosides and the MIC for a microorganism (e.g. for most of the patients in internal medicine it would be MIC = 1 mg/L) and using the population parameters has shown 90% success in pneumonia therapy [18,19]. With the parameters obtained here, similar success rates were observed in simulations.

In view of the concentration-dependent bactericidal activity of aminoglycosides and the presence of a post-antibiotic effect, it has been suggested that less frequent administration of larger doses may maximise bacterial killing activity [16]. Simulations were performed with the currently prevailing once-daily regimen of 7 mg/kg and by sampling from the comprehensive population distributions obtained here. The simulations show that using the parameters and their variabilities and knowing the PDI for the target microorganism, 90% of the patients in the once-daily regimen would be within the therapeutic range for C_{peak}/MIC (for MIC = 1 mg/L) [4]. A two-fold improvement in the precision of targeting appears possible when the patient-specific clearances are used, based

on the individual CrCL, as observed earlier for AUC/MIC [31]. However, besides improvement in precision, the absolute magnitudes of the AUC/MIC PDI should be adjusted for each microbial species and for the patient-specific CL. Efforts should aim at further exploring adequate MIC-dependent PDI markers [32,33]. Then, with the use of bicompartmental population parameters and covariate models, a reduction in the risk of inappropriate therapy can be achieved.

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