Pharmacokinetics of Teicoplanin in an ICU Population of Children and Infants

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Purpose. Better dosing is needed for antibiotics, including teicoplanin (TEI), to prevent emergence of resistant bacterial strains. Here, we assess the TEI pharmacokinetics (PK) related to a 10 mg/l minimum inhibitory concentration (MIC) target in ICU children (4 to 120 months; n = 20) with gram+ infections.

Methods. Standard administration of TEI was with three 10 mg/kg Q12h, loading infusions, and maintainance with 10 mg/kg or 15 mg/kg Q24h. During maintenance, 9 samples (3/day) were collected per patient and the PK analyzed with Nonlinear Mixed Effects Model (NONMEM).

Results. Thirty-five percent of concentrations in older children (≥2 months) vs. 8% in younger infants (<12 months) were below the target MIC. The global bicompartmental population PK parameters were [mean (interindividual CV%)] CL = 0.23 l/h [72%], V = 3.16 l [58%], k_{12} = 0.23 h^{-1}, and k_{21} = 0.04 h^{-1}. Two PK subpopulations were identified. The older children had CL = 0.29 [23%] l/h, V = 3.9 l and the younger infants, CL = 0.09 [37%] l/h, V = 1.05 l. Residual error was reduced from 52% to around 30% in the final models.

Conclusions. Older children in the ICU may require relatively higher doses of teicoplanin. However, a study in a larger population is needed.

KEY WORDS: children; infants; NONMEM; pharmacokinetics; simulation; teicoplanin.

INTRODUCTION

Extended hospitalization increases the probability of infection with staphylococcal or enterococcal isolates, which is frequent for critically ill children (1). However, because of bacterial mutants surviving inappropriate antibiotic doses, strains of increasingly resistant gram+ and other bacteria have emerged, initially to β-lactam antibiotics, sulfonamides and quinolones and lately to the glycopeptides daptomycin, vancomycin and even teicoplanin (2–4). New antibiotics are becoming available against gram+ resistant strains (5), particularly against *Staphylococcus aureus*, but it is unlikely that glycopeptides will be phased out soon. Instead, the consensus is to focus on the prevention of resistant strains, through less arbitrary titration of therapy (6), else the same resistance emergence cycle could repeat with the new classes.

Teicoplanin (TEI), produced by *Actinoplanes teichomyceticus*, is a glycopeptide chemically related to vancomycin introduced in 1984 (7). It acts through inhibition of bacteria cell wall synthesis via binding to the terminal acyl-D-alanyl-D-alanine residue of the cell wall peptidoglycan. The drug has demonstrated *in vivo* and *in vitro* efficacy against aminoglycoside and vancomycin resistant strains of gram+ aerobic and anaerobic bacteria (7,8), although there is still inconsistency regarding resistance emergence and susceptibility between the "*in vitro*" and "*in vivo*" media (9).

The marketed drug is a mixture of 10 related hydrophilic components predominantly bound to albumin in plasma (overall binding is 90%) and eliminated unchanged by glomerular filtration while only 2–3% is metabolized when given intravenously. TEI is not absorbed orally, and penetrates slowly the gastrointestinal tract and the cerebrospinal fluid (10). In patients with normal renal function tricompartmental pharmacokinetics (PK) have been described after intramuscular or intravenous administration (7,10,11) with rapid distribution in muscle and soft tissue, and in epithelial, pleural, and synovial fluids followed by slow elimination allowing once- daily administration. Additionally, TEI appears to have lower nephrotoxicity in children compared to vancomycin (12).

Significant efforts are made lately to determine pharmacokinetic/pharmacodynamic (PK/PD) indices best related to the efficacy of antibiotic therapy. The total time over which drug concentrations remain above the minimum inhibitory concentration (MIC), ($T_{>MIC}$), or the Cmax/MIC ratio appear most significant in animals for once-daily glycopeptides (13). However, these goals, *in vivo* and in humans, may be hampered by variability, in repeated dosing antibiotic therapy, even after the same dose (11,14). Difficulties also could exist due to the apparent differences in the PK between infants and children which have not been studied for teicoplanin (15,16).

In the current study, we performed a mixed effects, population, PK study of children aged 4 to 120 months, treated with TEI in the pediatric ICU for gram+ infections. Population covariate regression was used to explore the relationship of the PK with the covariates. Finally, we used Monte Carlo simulation from our parameter distributions to explore the typical expected concentration ranges and also simulated trial therapeutic regimens for children or infants, with the putative 10 mg/l MIC target for *S. aureus*.

MATERIALS AND METHODS

Patients

This was an open, prospective, randomized design study, performed in a 10-bed multidisciplinary Pediatric Intensive Care Unit (PICU) and included critically ill children admitted to the PICU with developed gram+ infection. Patients with metabolic diseases, renal (serum creatinine > 1.2 mg/dl) or hepatic insufficiency (serum aspartate aminotransferase [AST] or alanine aminotransferase [ALT] more than twice normal) were excluded from the study.

After approval by the Ethics Committee of the hospital and written informed consent by legal guardians, eligible pa-

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tients were randomized to receive either 3 loading doses of TEI (10 mg/kg i.v.) every 12 h (Q12h) followed by once daily doses (Q24h) of 10 mg/kg (n = 10) or the same loading dose followed by maintenance of 15 mg/kg Q24h (n = 10). TEI was administered as a 1-h infusion.

At the time of enrollment each patient had medical history and demographic details recorded. A physical examination, radiologic bacteriological and laboratory tests were performed. Blood was obtained every 24 h for cultures and for the determination of serum urea, creatinine, electrolytes, AST, ALT, total and direct billirubin, alkaline phosphatase, total protein, albumin, C-reactive protein, full blood count prior to TEI administration and every 48 h afterward, until the end of the study. Urinalysis was daily performed and chest radiograph was carried out as clinically indicated.

Blood samples (1–2 ml) were taken for the determination of TEI before and after the 1st, 3rd, and 5th maintenance dose (1 h before, 1 and 3 h after each dose). The blood was left to clot and centrifuged for 20 min. The serum was separated and stored at –70°C until analysis.

TEI plasma concentrations were determined with a fluorescence polarization immunoassay (FPIA) method in a TDx analyzer with Innofluor teicoplanin reagents (Seradyn Inc., Indianapolis, IN, USA). The teicoplanin calibrators, provided with the kit, offer an assay range of 0–100 mg/l. Accuracy involves recovery of 94–110% and a control set of 3 levels of concentrations. The coefficient of variation ranged from 1.7 to 4.2% intra-assay and 2.4 to 6.7% inter-assay. The sensitivity of the test was 1.18 mg/l.

Pharmacostatistical Models

Preliminary Standard Two-Stage (STS) method fits were performed for comparison between the structural PK parameters at the 10 mg/kg and 15 mg/kg dose levels (n = 10 each). NONMEM was used for obtaining the first stage individual estimates and standard methods for obtaining the second stage mean and deviations. The STS method was also used for testing the distributions for the two age subpopulations separated before and after 12 months. Once PK linearity was established all runs were population parametric estimation runs.

The observations were described by

$$Cp_{ij} = f(q_i, t_{ij}, D_i) + \varepsilon_{ij}, \quad (1)$$

where Cp_{ij} are the concentration values, and $f(q_i, t_{ij}, D_i)$ is the PK model with parameter vector $\mathbf{q}_i$ (p × 1 vector for p parameters) at times t_{ij} and (infusion) dose D_i for the *i*th individual at the *j*th time. Tri, bi, and mono compartmental models were tested. The residual, stochastic or "noise" matrix elements, ε_{ij} (EPS or ERR in NONMEM) were modeled as normal independently and identically distributed with mean $E[\varepsilon_{ij}] = 0$ and variance $Var[\varepsilon_{ij}] = \sigma_\varepsilon^2 f^2(q_i, t_{ij}, D_i)$, (proportional model). σ_ε is a fixed effect coefficient of variation to be determined and includes assay error, model misspecification and unspecified temporal variation of the parameters $\mathbf{q}_i$ during the study.

A lognormal distribution was assumed for the parameter elements q, CL, V, k_{12}, and k_{21}. So the second stage model is,

$$q_i = \bar{q} \exp(\eta_i^q), \quad (2)$$

where the overbar marks the typical value for the study population and $\boldsymbol{\eta}$ (ETA), the inter-individual random effect p × 1 vector, is assumed to be distributed as a multivariate normal $N(0,\omega^2)$. Hence, the parameters $\mathbf{q}$ are distributed as the lognormal $LN(\mu,\omega^2)$, where μ, (p × 1) is the fixed effect population mean (geometric mean for the transfer rates) vector, and ω (OMEGA) is a p × p lower diagonal variance-covariance matrix.

A fundamental criterion for all NONMEM runs was the successful estimation of the covariance matrix, and of the standard error (SE) of the estimates of the fixed and random effects.

A Monte Carlo (MC) sampler coupled to a bicompartmental PK model was used to simulate PK profiles in virtual patients after a single infusion dose of TEI. The method first draws a large sample from the population parameter distributions (e.g., 10,000 sets of CL, V, k_{12}, and k_{21} representing an equal number of virtual patients). Then the PK model is used to simulate that number of the expected concentration time courses and obtain robust statistics, that is, confidence interval ranges for the concentrations, percentage of target attainment, and so forth.

Covariate Modeling

In mixed effects regression, the fixed effect marginal parameter $\bar{q}$ is expanded to include covariates (COV = Weight, Age) with fixed effects (θ) as coefficients as, $\bar{q}_c = \theta_1 * (1 + \theta_2 COV)$, then Eq. 2 becomes $q_i = \bar{q}_c \exp(\eta_i^q{}_c)$ and $\eta_i^q{}_c$ should now come from a distribution with an *unexplained* variance component ω_c^q, which should be smaller than ω^q for the same structural model. Age and weight were used as patient covariates.

Statistics

Differences between covariates and parameters in population groups were tested with the unpaired *t* test (two-sided at the $p < 0.05$ significance level). AUC and odds ratios (OR) and the χ^2, for the OR and $CI_{95\%}$, were calculated by counting, aided by GraphPad InStat (GraphPad Software Inc., San Diego, CA, USA). Covariate plots and trends were obtained in MS Excel (Microsoft Corporation, Seattle, WA, USA). Testing for subpopulations was performed with NONMEM mixture models and OR of the obtained frequencies.

Model Diagnostics

The distributions of weighted residuals (WRES), testing for non-skewness, and goodness-of-fit of populations (PRED) and individual (IPRED) predictions vs. observations were used for model fit diagnosis. The correlations between parameters obtained in the corresponding matrix in NONMEM were also used for diagnosis. Comparison between models, differing in one parameter only, used the objective function reported by NONMEM, which is the negative of twice the logarithm of the likelihood of the parameters (–2LLD) given the data. Differences between successive –2LLD are asymptotically χ^2 distributed (NONMEM user's manual part VI) with a change of 7.8 in –2LLD significant at the $p < 0.005$ level for one degree of freedom. Additionally, the 95% confidence interval of the covariate coefficient- a fixed effect- was evaluated as $CI_{95\%}$ = {mean – 1.96 * SE, mean + 1.96 * SE} and if it included zero the particular form

was rejected (e.g., additive vs. power exponent on weight). The correlation matrix for the parameter estimates, as output by the package, was also checked.

RESULTS

Patients

Twenty-five consecutive patients with bacteriologically documented gram+ infection were candidates for the study. Five patients were excluded from the analysis, two with metabolic disease, two with renal failure and one with hepatic dysfunction. Among the 20 remaining patients aged 4 months to 10 years, 11 were boys and 9 were girls. Four children were under 12 months of age. All patients had albumin levels within normal levels with little variation (mean ± SD: 3.5 ± 0.8 g/dl). Random assignment into 10 mg/kg and 15 mg/kg groups fortuitously—as age separation was after PK modeling—resulted in two younger infants (<12 months of age) in each group (IDs 2 and 9 and IDs 11 and 12, respectively).

Briefly, in the10 mg/kg group, 7 patients had *Staphylococcus epidermis* (*S. epidermidis*) sepsis, 1 *Enterococcus fecium* (*E. fecium*) sepsis, and 2 methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia. In the 15 mg/kg group, 9 children had sepsis (6 with *S. epidermidis*, 2 with MRSA, and 1 with *E. fecium*) and 1 had MRSA pneumonia. Initial entrance pathologies were head injury (n = 6), pneumonia (n = 3), epilepsy (n = 2), multiple trauma (n = 2), and individual cases of poisoning, drowning, burn, intracranial hemorrhage, encephalitis, and foreign body aspiration.

No clinical or functional toxicity was associated with the administration of TEI and no patient presented alteration of renal or hepatic function during the therapy. Only one patient developed skin rash in the second day of treatment, which disappeared a few hours later. TEI therapy was continued without modification in the therapeutic program for approximately 10 days. All patients were cured from the gram+ infection, and no relapse was noted during their hospital stay.

Pharmacokinetic Model

Figure 1 shows the observed concentration evolution in two age groups of children separated around 12 months of age. The mean bicompartmental models for each dose schedule (10 or 15 mg/kg TEI Q24h) are shown. In preliminary linearity testing with Two Stage fits for each dose group separately, no statistically significant difference was found in the PK parameters between the 10 mg/kg (n = 10) and 15 mg/kg groups (n = 10) (for CL and V; p = 0.99 and p = 0.61, respectively and for the transfer rates, k_{12} and k_{21}, p = 0.2 and 0.5, respectively). No significant differences were detected in the trough concentrations between dose groups, at least within the sampled three PK cycles (p = 0.5).

However, a dichotomous difference was observed relative to a MIC of 10 mg/l and a grouping based on age became evident upon inspection. The frequency of observations below that MIC was 35% for children over 12 months of age and 8% children below that age. Hereon, the former age group is labeled "older children" and the latter "younger infants" (infants are ages 0 to 24 months). Nevertheless, the OR of Cmin below or above 10 mg/l between age groups was not significant (OR = 6; χ^2 = 3.35; p = 0.07).

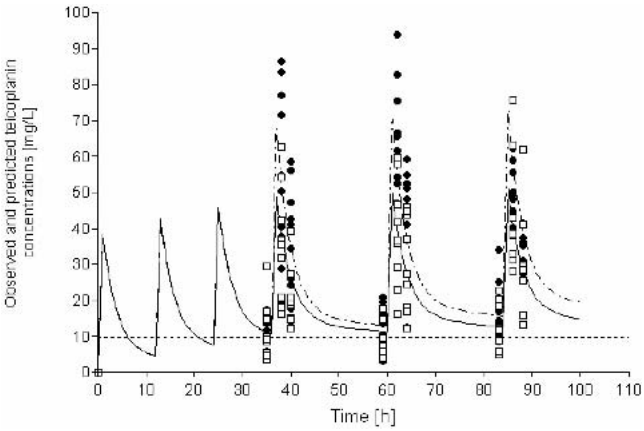

Fig. 1. Teicoplanin plasma concentration (Cp) observations in younger infants (<12 months old; solid circles) and older children (12 months to 10 years; open squares) after doses of 10 and 15 mg/kg, both with the same loading. The typical population bicompartmental prediction in a child of mean weight (14 kg) is shown for the complete therapeutic regimen: 3 × 10 mg/kg Q12h loading dose and 10 mg/kg Q24h maintenance (solid line), and 3 × 10 mg/kg loading and 15 mg/kg maintenance (dash-dotted line). The straight line is the upper limit MIC target for *Staphylococcus aureus*.

Table I lists the demographic and observed kinetic characteristics for the 20 children and the two sub-populations separated by age. The minimum and maximum concentrations (Cmin, Cmax) observed in the three cycles as well as the area under the concentration vs. time curve from the first (35 h) to the last time point (AUC35-last) are listed. There are appreciable, yet non statistical, differences in the mean and median values between the two age groups.

Table I. Demographic Characteristics, Observed Concentration Extremes, and $AUC_{35-last}$ in 20 Children (all, n = 20) and Separately in Groups of Younger Infants (<12 months, n = 4) and Older Children (≥12 months, n = 16)[a]

	Medium	Mean (SD)	Range
Age (months), all	21.5	37.6 (35.4)	4–120
<12 months	7.5	7 (1.9)	4–9
≥12 months	33	45.2 (35.7)	12–120
Weight (kg), all	14	14.3 (6.2)	4–28
<12 months	5.5	5.7 (1.5)	4–8
≥12 months	14.5	16.4 (5)	11–28
Dose (mg), all	170	177 (92.7)	40–420
10 mg/kg group	135	133 (54.5)	40–220
15 mg/kg group	210	221 (101.8)	60–420
<12 months	55	73 (31.5)	40–120
≥12 months	190	203 (84.2)	110–420
$AUC_{35\text{-last}}$ (mg h/l), all	1115	1194 (410)	519–1889
<12 months	1557	1484 (315)	1048–1775
≥12 months	1080	1121 (406)	519–1889
C_{max} (mg/l), all	61.35	59.9 (18.8)	23.6–93.9
<12 months	70.75	71.8 (9.3)	62.7–83
≥12 months	54.9	56.9 (19.5)	23.6–93.9
C_{min} (mg/l), all	9.85	9.01 (4.3)	3.1–16.8
<12 months	12.85	12.1 (4.6)	5.8–16.8
≥12 months	8.45	8.24 (4)	3.1–14.1

[a] Doses were either 10 mg/kg (n = 10) or 15 mg/kg (n = 10) with no statistical difference in the concentrations or the pharmacokinetic parameters.

The data were insufficient for resolving a three compartment system, so a bicompartmental PK model was selected for explaining the time course of Cp observations, after comparison of the objective function and residual plots with monocompartmental descriptions.

The NONMEM first-order (FO) method, although apparently successful, under scrutiny, proved highly inconsistent for the problem. This was judged by the FO not identifying outliers in the residual magnitudes and by showing inconsistency in the fixed effect parameter estimates after changes in the error model or after removal of single outlying residuals. The standard FO conditional estimation (FOCE) method was more reliable, but did not produce the covariance estimate in most occasions. The full Laplacian approximation to the marginal likelihood proved optimal (satisfying all the preset criteria) for this problem. Estimates of the basic population PK parameters from the Laplace method, before segregation by age (n = 20), are shown in Table II for a model estimating the micro rates k_{12} and k_{21}, and for a model estimating the more physiologic parameters Q and V2 (apart from CL and V). The –2LLD for the former was 1043.035 and 1072.55 for the latter.

There was high correlation between the variabilities of CL and V. This is due, in part, to the single predose trough observations (at 35 h) and the final near-the-peak observations (at 85–88 h) which were unpaired with peak and trough Cps in their own cycles, respectively. Thirty percent of all observations were in these frames. Consequently, because CL is better determined at the troughs and V, k_{12}, and k_{21}, near the peak, covariance with the remaining parameters from these cycles is increased.

Covariate Models

In preliminary graphical and regression analyses, body weight (WT) was well predicted by age via a logarithmic relationship (WT = 6.19 × Ln(age) – 5.5; r^2 = 0.89). Similarly, age plotted against CL or V showed a discontinuity around 12 months of age. WT also showed a linear relationship with CL and V, under 12 months, and then logarithmic behavior beyond that age. However, linear and nonlinear models of CL and V with WT attempted in NONMEM failed. Instead, weight-scaling of CL and V was successful (–2LLD = 982.88, a significant difference) and the model is listed in Table III, with a sharp reduction in the unexplained interindividual variance for CL and in the residual prediction error. When age was entered as a continuous (linear and nonlinearly related) covariate, there was slight or no improvement in the fits. In contrast, the population split in two age categories, within the same fit gave a successful model (–2LLD = 971.347), also listed in Table III with further reduction in the residual error. This age model allowed a true estimate of the variance for V.

Table II. Teicoplanin Basic Bicompartmental Population (NONMEM) Parameters and Standard Deviations (SD) with Standard Errors of the Estimates (SE)[a]

	Typical value (SE)	SD (SE)	CV%
Basic model	(–2LLD = 1178.35)		
CL (l/h)	0.23 (0.12)	0.16 (0.03)	72%
V (l)	3.16 (0.46)	1.83[b]	58%
k_{12} (h^{-1})	0.23 (0.025)	0.06[b]	26%
k_{21} (h^{-1})	0.04 (0.016)	0.02[b]	50%
Q (l/h)	0.32 (0.07)	—	—
V2 (L)	4.7 (0.41)	—	—
σ (CV%)	52% (26%)	—	—
$t_{1/2\alpha}$ (h)	2.0	—	—
$t_{1/2\beta}$ (h)	79.3	—	—
$t_{1/2\,k10}$ (h)	9.5	—	—

[a] The parameters are from two distinct models and runs parameterized with either CL, V, k_{12}, and k_{21} or CL, V, Q, and V2. The corresponding coefficient of variation percent (CV% = 100*SD/Typical value), alpha and beta phase half-lives ($t_{1/2\alpha}$, $t_{1/2\beta}$), as well as the central compartment half-life ($t_{1/2\,k10}$) are calculated and listed.
[b] From Two Stage fits.

Infants Below and Children Above or Equal to 12 Months of Age in the Population

Inspection of the concentration evolution profiles (Fig. 1) as well as histograms of the individual PK parameters suggested a bimodality or a dichotomous difference in the central parameters. Because one of the parameter modes contained very few points (younger infants), further methods were used to test for dichotomy within PK modeling.

The NONMEM program implements a statistical "mixture" model at the interindividual variance modeling stage, also applied here. The mixture model assigns individuals, depending on their PK parameters, into subpopulations with frequency p (and 1 – p for the remaining subjects). The model consistently indicated the presence of a subpopulation with proportion p = 15%. This subgroup, remained stable in all error models attempted, and contained 3 out of the 4 infants and none of the older children. There were significant odds that a younger infant would have PK parameters from a distinct distribution from the rest of the children [OR = 45; $CI_{95\%}$: 2.2 – 940; χ^2 = 9.45; p = 0.002]. None of the fits concluded with standard error estimation, most likely due to the reduced population sizes, so we do not report the parameters here. However, all estimates were of the same order as in the rest of the analysis and different between the two age groups. This analysis rigorously indicated a separation of the population into two age groups: (a) ages under 12 months—younger infants—(n = 4), and (b) 12 months of age or older to 10 years—older children—(n = 16)

Subsequently, the basic micro-constant model was applied to each subpopulation apart. The Laplacian method was successful even in the reduced population (SEE estimate), although the $CI_{95\%}$ test failed for one of the micro constants in each group. The PK parameters were significantly different between age groups and so were the interindividual variabilities for CL. Results from this step are listed in Table IV. Figures 2(a)–2(c) show the population predictions vs. observed concentrations of teicoplanin in the entire group and the two subgroups, respectively. The spread is quantified with the r^2, listed in the frames. As seen, the separation into the older children group improves the fits from r^2 = 0.21 to 0.55.

MC simulations of the profiles of expected TEI concentrations (10 time points) were performed extracting 10,000 virtual patients and shown in Fig. 3 with 68% confidence intervals. Simulations were after the mean doses of 170, 55, and 190 mg TEI for each group, respectively (Table I). Samples were extracted from the three sets of population PK parameter distributions (Tables II and IV), and bicompart-

Table III. Final Population Covariate Models for PK Parameters as Functions of Weight and Age[a]

Weight corrected	(−2LLD = 982.886)		
CL (l h^{-1} kg^{-1})	0.017 (0.008)	0.005 (0.003)	30%
V (l/kg)	0.26 (0.03)	—	—
σ1 (CV%)	33% (13%)	—	—
Age as subgroup (categorical) covariate	(−2LLD = 971.347)		
Age ≥12 months			
$CL_{>12}$ (l/h)	0.26 (0.13)	0.1 (0.03) l/h	40%
$V_{>12}$ (l)	4.17 (0.54)	1.9 (1.08) l	45%[b]
Age <12 months			
CL [= $CL_{>12}$ * 0.14 (0.08)[c]]	0.04 l/h	Same as above	
V [= $V_{>12}$ * 0.34 (0.12)]	1.43 l		
σ1 (CV%)	26% (12%)	—	—

[a] The transfer rates are nearly identical to the basic model and not listed here.
[b] Mixed effects estimate of the SD for V.
[c] $CI_{95\%}$ contains zero.

mental PK model runs were performed for each of 10,000 samples (lines in Fig. 3). No covariance among parameters was assumed. The mean predicted profiles for the three populations are marked with symbols. The total population is also the outer envelope (solid lines). The two subgroups have reduced 68% likelihood intervals (dashed and dash-dotted lines). Mean profiles are coincident above the MIC but diverge below that. We observe that this standard regimen leads to profiles around the target, but the spread around the mean is remarkable, even at a 68% confidence. The probabilities of attainment of a target are different among the subgroups. Particularly, for children of ages 12 to 120 months (dash-dotted line), the regimen is likely to have initial troughs below the tentative 10 mg/l MIC most of the time or, in an alternative interpretation, this is likely to be so in most of the children. In younger infants less nearly half of the patients are likely to be above that target.

Table IV. Bicompartmental Population Pharmacokinetic Parameters for Teicoplanin for Younger Infants (<12 Months) and for Older Children (12 Months to 10 Years) with Standard Error (SE) and Coefficient of Variation (CV) of the Typical Value for Central Clearance (CL)[a]

	Typical (SE)	SD (SE)	CV%
Age <12 months	(n = 4)		
CL (l/h)	0.09[b] (0.02)	0.033 (0.023)[c]	37%
V (l)	1.05 (0.04)	—	—
k_{12} (h^{-1})	0.35 (0.25)[c]	—	—
k_{21} (h^{-1})	0.10 (0.07)[c]	—	—
σ (%)	34% (16%)	—	—
$t_{1/2\,k10}$ (h)	8.1		
Age ≥12 months	(n = 16)		
CL (l/h)	0.29 (0.12)	0.09 (0.06)[c]	23%
V (l)	3.9 (0.51)	—	—
k_{12} (h^{-1})	0.23 (0.02)	—	—
k_{21} (h^{-1})	0.03 (0.12)[c]	—	—
σ (%)	32% (12%)		
$t_{1/2\,k10}$ (h)	9.32		

[a] The population dispersion of the distribution could not be determined for the remaining parameters. The central compartment half-life ($t_{1/2\,k10}$) is calculated and listed.
[b] Significantly different populations for CL and V at $p < 0.005$.
[c] $CI_{95\%}$ contains zero.

Figure 4 shows a mechanistic simulation of the current standard regimen in the two most extreme subjects of our population (by age and WT) for both older children (solid lines) and infants (dotted lines). The envelopes diverge visibly since the first dose.

Subsequently, simulations were performed to determine a regimen producing similar levels in both subgroups as observed here. Figure 5 shows a simulation in the same population extremes as above, but for an alternative regimen with infusions of 1 h duration, as 5 mg/kg loading followed by 4 mg/kg, Q24h, for infants, and 10 mg/kg loading followed by 8 mg/kg, Q24h, for older children. In the simulation, younger infants required nearly half the dose of older children to achieve similar therapy.

DISCUSSION

TEI exhibits bactericidal activity against aerobic and anaerobic gram+ bacteria, but emerging resistant strains, particularly of *S. aureus*, constitute a challenge (1,3). More sophisticated titration of teicoplanin can pay off, in the long term, by reducing survival of resistant mutant strains of bacteria (6).

In this study, we analyzed TEI concentration observations from PICU children with gram+ infections under repeated dosing. A bicompartmental PK, mixed effects, model described optimally the observations from monitoring with a $t_{1/2\beta}$ of 79 h Two dosing schedules were used (10 and 15 mg/kg Q24h) and their kinetics were within linearity. However, when the evolution was compared graphically a duality was seen, related to age rather than regimen. The frequency of occurrence of Cmin below the MIC of TEI for *S. aureus* (10 mg/l) was higher in children over 12 months of age, compared with that in infants (35% vs. 8%, respectively), independent of dose. A distribution mixture model, as implemented in NONMEM, indicated the existence of a subgroup of four children (3 younger infants and 1 older child). Subsequent covariate analysis, verified an age related dependence in the PK. Age related changes in the PK of hydrophilic antibiotics are known to exist (15,16).

Literature values of the β half-lives ($t_{1/2\beta} = \ln 2/\beta$), vary from 2.9 to 15.4 h, and the longer $t_{1/2\gamma}$, varies from 87 to 168 h (3,7,8). Interestingly, here, the terminal elimination half-lives (corresponding to bicompartmental PK) were all of the same order as in adults. The global $t_{1/2\beta}$ was 79 h. The $t_{1/2\beta}$

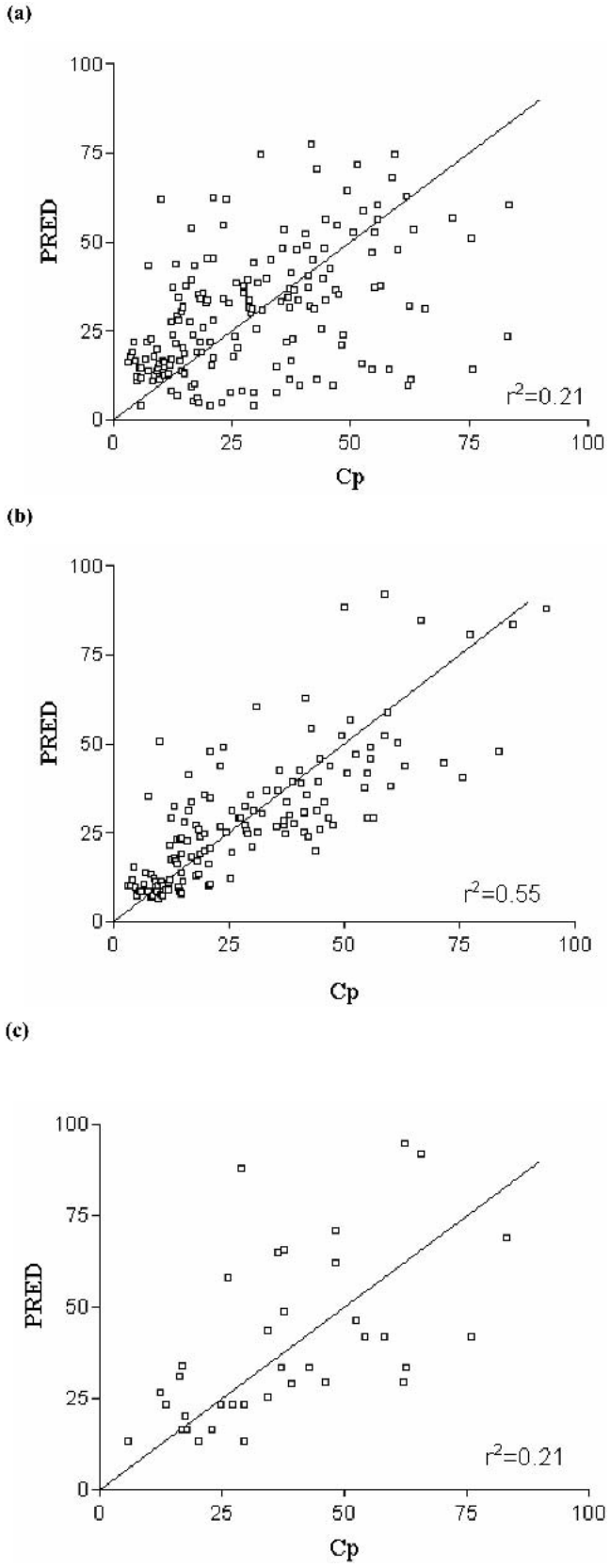

Fig. 2. Population predicted (PRED) vs. observed (Cp) teicoplanin plasma concentrations in the entire group (n = 20) (a), the older children (n = 16) (b), and the younger infants (n = 4) (c).

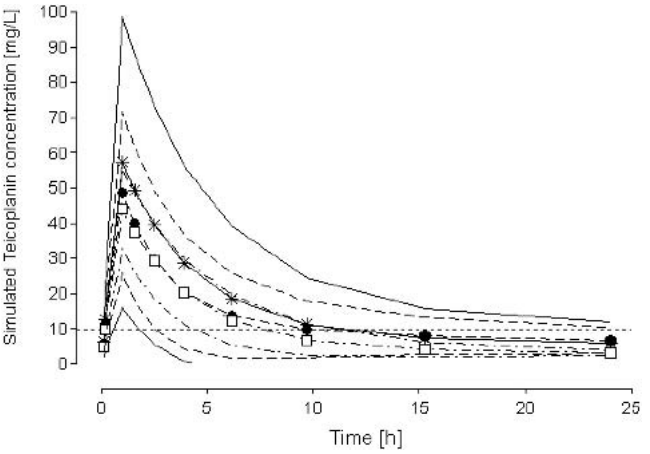

Fig. 3. Expected concentration time courses for teicoplanin with corresponding 68% confidence intervals in 3 populations (global, younger infants and older children), each with 10,000 simulated patients via Monte Carlo sampling from the corresponding distributions (Tables II and IV). Doses are the median for each group (Table I). The mean profile ± 68% envelopes (means marked with symbols) are shown as solid lines for the global population (stars), dashed lines for the younger infants (solid circles), and dash-dotted lines for older children (open squares) population. The target MIC of 10 mg/l is shown as a straight line. Note how for the older children (dash-dot lines), the entire 68% percent envelope falls below the MIC half way through the cycle.

partitioned by age above or below 12 months, tentatively estimated with the parameters k_{12} and k_{21} whose $CI_{95\%}$ contained zero (Table IV) were of similar orders of magnitude (80 to102 h). Similarly, the central compartment half-lives, $t_{1/2\,k10}$ ($k10 = CL/V$), were nearly identical between the global and the sub populations. Therefore, at the half-life level it would appear that there were no differences between groups.

However, our compartmental PK parameter estimates in children exhibit an increase in weight-normalized values but

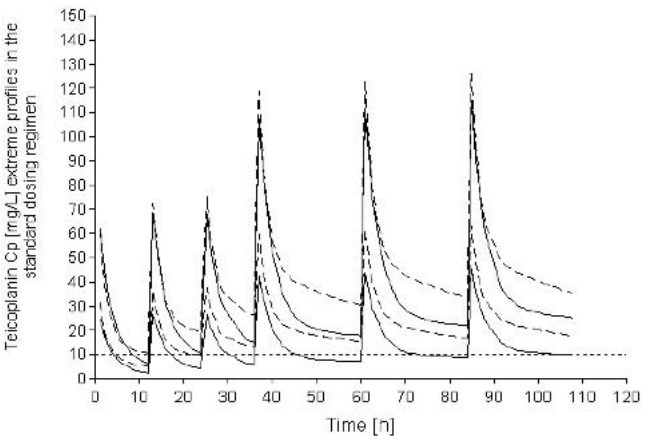

Fig. 4. Evolution of teicoplanin plasma concentration in the two most extreme subjects from the study population (n = 20) and for the standard regimen of 3 × 10 mg/kg loading + 15 mg/kg maintenance (3 cycles shown) after simulation with PK parameters sampled from the two subpopulations [infants under 12 months (dotted lines) and older (solid lines)]. Individualization is by age (in the PK parameters) and weight (in the dose). The straight line is the tentative target against *S. aureus*.

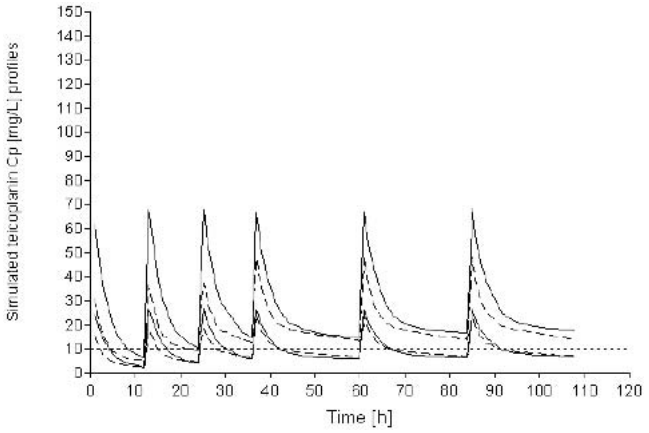

Fig. 5. Simulation of mechanistic extremes, as above, but loading (3× Q12h) and maintenance (Q24h) doses are, for infants, 5 mg/kg and 4 mg l^{-1} kg^{-1}, and for older children, 10 mg/kg and 8 mg l^{-1} kg^{-1}, respectively.

a significant decrease in absolute magnitudes, compared to the values reported for the adults (10,11). The initial volume of distribution (V) was 0.26 l/kg and the clearance (CL) was 0.017 l h^{-1} kg^{-1} or for the mean weight of 14 kg, 3.16 l and 0.23 l/h, respectively. The reported values in adults (for tricompartmental fits) are 7 l and 0.8 l/h. Importantly, in our population, younger infants show a 3-fold reduction in V and CL. As a consequence, after infusion dosing the Cmax and the AUC were elevated in children under 12 months compared with children over 12 months whose average Cmin was reduced below 10 mg/l. This age dependent difference could be related to the complex, active and passive, disposition of TEI and the tissue growth process in young age. *In vitro* homogenate studies suggest that TEI binds to cell membrane, but only enters some cells. Because "*in vivo*," only a small fraction of the total cell surface area is exposed to the perinusoidal space where exchange occurs (17), a difference may exist at that level between infants and children and explain the reduction in V in infants.

The therapeutic outcome has been related mostly to trough levels but also to the AUC and Cmax. In a mouse peritonitis model, it was determined that the length of time over which serum concentrations remain above the MIC ($T_{>MIC}$) and the ratio Cmax/MIC were the main indicators of therapy with nearly equal significance (8) with a ratio of Cmax/MIC at least equal to 4, considered adequate for therapy. Once a trough target is set, the success of therapy will correlate with the corresponding peaks as well, unless the infection site is diffusion dependent (e.g., in endocarditis) or there is significant alteration in albumin levels (e.g., renal insufficiency). In any case, because therapeutic efficacy depends on Cmin, Cmax, and AUC, hence on the PK parameters rather than the half-life alone, a reassessment of the standard dosing paradigm may be needed.

In our case, although the 15 mg/kg regimen provided better attainment of the target Cmin, the two populations had very different probabilities of attainment. This was crudely appreciable in the observations, where only 8% of levels in the infants fell below the MIC compared to 35% in the older children. Indeed, as observed after MC simulation with 10,000 samples, the infant subpopulation had adequate therapy even in patients whose PK parameter(s) (one or more) were over 1 SD away from the population mean.

Further, simulations were performed of the complete regimen (loading + daily doses) in order to improve long term stability above 10 mg/kg of TEI concentrations. It appears that younger infants are adequately treated when receiving half the dose of older children. For example, for the infants, loading doses of 5 mg/kg (3× Q12h) followed by 4 mg/kg (Q24h) maintenance, and for older children, loading with 10 mg/kg (3× Q12h) followed by 8 mg/kg (Q24h) maintenance, would keep both age groups within the same Cmin range.

In conclusion, we have observed a possible age related dichotomy in the microscopic (V and CL) but not the macroscopic (half-life) PK parameters between older children and younger infants, which could, otherwise, have been attributed to variability in the kinetic behavior. We found that, under standard protocol, the expected troughs for children between 12 months and 10 years of age, as simulated from our population PK parameter distributions, were more likely to be undertherapeutic than in infants below 12 months of age. Still, a PK study is needed in a larger population under TEI therapy, with equal numbers of younger infants and older children.

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