Using population pharmacokinetics to dose gentamicin during extended-daily diafiltration in critically ill patients with acute kidney injury

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Short Title – Gentamicin pharmacokinetics during EDD-f
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Abstract

The objective of this prospective pharmacokinetic study was to describe the variability of gentamicin plasma concentrations in critically ill patients with AKI necessitating extended-daily-diafiltration (EDD-f) using a population pharmacokinetic model and to subsequently perform Monte Carlo dosing simulations to determine which dose regimen achieves pharmacodynamic targets most consistently. We collected data from 28 gentamicin doses in 14 critically ill adult patients with AKI requiring EDD-f and therapeutic gentamicin. Serial plasma samples were collected. A population pharmacokinetic model was used to describe the pharmacokinetics of gentamicin and perform Monte-Carlo dosing simulations between 3mg/kg and 7mg/kg and at various time points before commencement of EDD-f to evaluate the optimal dosing regimen for achieving pharmacodynamic targets. A two-compartment pharmacokinetic model described gentamicin clearance on and off EDD-f adequately. The plasma half-life of gentamicin during EDD-f was 13.8-hours compared with 153.4-hours without EDD-f. Monte-Carlo simulations suggest that 48-hourly 6mg/kg dosing either 30-minutes or one-hour before the commencement of EDD-f results in 100% attainment of Cmax (<10mg/L) targets and sufficient attainment of AUC_{0-24} (70-120 mg.h/L) targets. None of the simulated dosing regimens achieved satisfactory Cmin targets (<1.0mg/L) at 24-hours. In conclusion, dosing gentamicin 30-minutes to one-hour before the commencement of an EDD-f treatment enables attainment of target peak concentrations for maximal therapeutic effect, whilst enhancing drug clearance to minimize toxicity. Re-dosing in many patients should occur after 48-hours and we would recommend use of therapeutic drug monitoring to guide dosing to optimize achievement of AUC_{0-24} targets.
Introduction

Acute kidney injury (AKI) is an independent risk factor for mortality in critically ill patients (5) and has a mortality rate as high as 60% (20). Of all patients admitted to a critical care unit, approximately 5% will develop AKI and at least 70% of these patients will require renal replacement therapy (RRT) (11). Extended-daily-diafiltration (EDD-f), also known as sustained-low-efficiency-dialysis, is an emerging form of RRT being increasingly used worldwide. EDD-f combines the convenience and efficiency of intermittent hemodialysis with the stability of traditional continuous renal replacement therapy into a 10-12 hour treatment (16). This ‘hybrid’ dialysis is reported to have advantages over intermittent hemodialysis and continuous RRT including efficient solute removal with minimum solute disequilibrium, improved hemodynamic stability, low anticoagulant needs, diminished cost and improved patient mobility (16). This has been confirmed in critically ill patients (1). However, drug dosing remains a challenge to critical care physicians with little pharmacokinetic studies undertaken to date with this specific dialysis modality (7, 10).

In critically ill patients, a wide array of pathophysiological changes can occur in patients which complicate antibiotic dosing (17). Changes in clearances and volumes of distribution for different dialysis treatments have been widely described although the number and type of dialysis modalities, and the consequent altered capacity for drug clearance necessitates pharmacokinetic studies be undertaken to determine the precise dosing requirements for a drug in the chosen dialysis modality (6). Such information is vital in the context of antibiotic dosing, particularly in patients with AKI who have higher mortality rates than other critically ill patients (5, 20).

Gentamicin is a widely used aminoglycoside antibiotic that has an important role in treatment of infections in critical care units. Gentamicin exhibits concentration-dependent bacterial killing
Further to this an area-under-the-concentration-time-curve from 0 to 24 hours ($AUC_{0-24}$) of 70-120 mg.h/L has been reported to be desirable for efficacy (4). Minimizing aminoglycoside toxicity in patients receiving gentamicin is best achieved by minimizing the minimum concentration during a dosing period ($C_{\text{min}}$). Emerging data supports maintenance of an $AUC_{0-24} \leq 120 \text{mg.h/L}$ to minimize toxicity as well (4).

**Aims**

To describe the variability of gentamicin plasma concentrations in critically ill patients with AKI necessitating EDD-f using a population pharmacokinetic model and to subsequently perform Monte-Carlo dosing simulations to determine a dose regimen that achieves pharmacodynamic targets most consistently.

**Materials and Methods**

**Patients**

This study was performed in a 13-bed intensive care unit of a 530-bed hospital. Ethical approval to conduct the study was obtained from the local institutional ethics committee (protocol 200620). Consent to participate was obtained from the patient’s legally authorised representative.

**Procedures**

Critically ill adult patients with AKI requiring EDD-f and therapeutic gentamicin treatment were studied. In accordance with usual practice, all patients had an indwelling arterial cannula. Patients were administered gentamicin at the discretion of the treating physician.
**Dialysis prescription**

EDD-f was performed in all patients with a Fresenius 4008S Haemodialysis machine (Fresenius Medical Care, Bad Homburg, Germany) using Fresenius AV600S filters (surface area 0.6m²; Fresenius Medical Care, Bad Homburg, Germany). For each patient, a central vein was cannulated with a standard dialysis vascular catheter. A standardised prescription consisted of hemodiafiltration with a target duration of 10 hours (300mL/min of blood and dialysate flow and with 50 mL/min predilution). The target duration was rarely achieved with EDD-f typically occurring for a duration of 6-hours. The biochemical composition of the dialysate and bicarbonate-based replacement fluid was set according to the patient’s biochemistry. Data on precise times for EDD-f commencement and cessation, due to blood clotting on filter or end of treatment, were recorded.

**Sample collection**

Gentamicin was administered by central venous line as a 30-minute infusion. Samples of arterial blood were collected from an indwelling arterial cannula, before the drug administration (T0) and at 15 minutes (T15), T30, T60, T120, T180, T300, T480 and at T600. Further arterial blood samples were collected from each patient to establish plasma concentrations between EDD-f sessions. Sampling occurred during the first dosing period and at subsequent dosing intervals where possible thereafter. EDD-f was commenced at the discretion of the clinician and did not uniformly correspond with timing of gentamicin dosing.

**Drug Assay**
Gentamicin plasma concentrations were determined using the SYNCHRON LX System assay (Beckman-Coulter Inc, Fullerton, USA). The within-run coefficient of variation was estimated as 7.1% at 2.2mg/L and 2.1% at 9.7mg/L. The lowest level of detection was 0.3mg/L.

**Pharmacokinetic and Statistical Analysis**

The concentration versus time data for gentamicin in plasma were analysed by a non-linear mixed effects modelling approach(2) using NONMEM (Version 6.1, GloboMax LLC, Hanover, MD, USA) with double precision with the COMPAQ VISUAL FORTRAN compiler. The Cmax and Cmin were the observed values from the intensive sampling schedule. The NONMEM runs were executed using Wings for NONMEM (WFN 6.1.3). Data were analysed using the first order conditional estimation method with INTERACTION.

For the population PK analysis, the plasma gentamicin concentrations were fitted to one, two or three-compartment linear models using subroutines from the NONMEM library(2). The concentration–time profile can be described as (Equation 1):

\[
y_{ij} = f_{ij}(\theta_i, x_{ij}) \cdot e^{\epsilon_{ij}} + \epsilon_{2ij},
\]

where \( y_{ij} \) is the \( j \)th observed concentration at time points \( x_{ij} \) for the \( i \)th subject. Also, \( \theta_i \) represents fixed effects parameter of the structural model to be estimated. \( f_{ij} \) is the function for the prediction of the \( j \)th response for the \( i \)th subject. Finally, \( \epsilon_{ij} \) denotes the \( j \)th measurement error for the \( i \)th subject. In other words, \( \epsilon_{ij} \) is the difference of the observed concentration from the predicted concentration. It is assumed to be independent and identically distributed with a normal distribution around the mean zero and variance \( \sigma^2 \).

Between-subject variability and between-occasion variability
Between-subject variability was modelled using an exponential variability model (Equation 2):

$$\theta_i = \theta \cdot e^{\eta_i}, \quad (2)$$

where $\theta_i$ is the value of the parameter for the $i$th subject, $\theta$ is the typical value of the parameter in the population and finally $\eta_i$ is a random vector with normal distribution, zero mean and variance–covariance matrix of between-subject variability $\Omega$ to be estimated.

**Model diagnostics**

To assess model validity, statistical comparison of nested models was undertaken in NONMEM based on a $\chi^2$ test of the difference in the objective function. A decrease in the objective function of 3.84 units ($P < 0.05$) was considered significant. Goodness-of-fit was evaluated by visual inspection of diagnostic scatter plots, including observed and predicted concentrations versus time, weighted residual versus time and residual versus predicted concentrations.

**Bootstrap**

A non-parametric bootstrap method (15) ($n = 1000$) was used to study the uncertainty of all pharmacokinetic parameter estimates in the final base model. From the bootstrap empirical posterior distribution we have been able to obtain the 95% confidence interval (2.5–97.5% percentile) for the parameters, as described previously (14).

**Covariate screening**

EDD-f was considered an essential covariate and therefore a base EDD-f model was established before other covariates were considered. The covariates analysed were age, total body weight (normalized to 70kg), lean body weight (LBW; equation from Janmahasatian et al (9)) normalized to 55kg, the final plasma creatinine concentration prior to commencement of EDD-f,
and creatinine clearance estimated via Cockroft-Gault equation (using total body weight) normalized to 6 L hr$^{-1}$ and adjusted aminoglycoside dosing weight.(3) Possible covariates were added in a stepwise fashion into the model. Covariates were considered for inclusion in the model if they were biologically plausible and there was improvement in the overall fit of the base model, i.e. decrease in objective function (at least 3.84 units), decrease in the unexplained between-subject variability of the parameter and decrease in residual unexplained variability.

**Dosing simulations**

Monte-Carlo dose simulations of different weight-based dosing regimens with differential delay between gentamicin dosing and commencement of a 10-hour treatment of EDD-f were undertaken using NONMEM. The simulations used a 50-years of age male (70kg total body weight and body mass index 23.6 kg/m$^2$) with daily doses of 3mg/kg, 4mg/kg, 5mg/kg or 7mg/kg administered either at the beginning of EDD-f (no delay), or 30-minutes, one-hour, 2-hours or 4-hours before EDD-f commencement. Simulations of 48-hourly dosing were also undertaken. Post-EDD-f dosing was not simulated in line with findings from a previous pharmacokinetic simulations paper by Teigen et al which demonstrated unacceptable gentamicin exposure when administered post-hemodialysis (18). Each Monte-Carlo simulation generated concentration-time profiles for 1000 subjects per dosing regimen using the parameters from the final covariate model. The ability of each dosing regimen to achieve pre-defined pharmacodynamic targets, Cmax:MIC ratio $\geq 10$ or AUC$_{0-24}$ 70-120 mg.h/L,(4) was then compared.
Results

Fourteen patients were enrolled, with 265 plasma gentamicin samples collected throughout 28 dosing intervals. All patients had sampling during the first dosing interval, with one patient having sampling from one additional EDD-f treatment, three patients having sampling during an additional two EDD-f treatments and two patients having sampling during an additional three EDD-f treatments. Patient demographic and clinical details are described in Table 1.

Population pharmacokinetic modeling was performed using the concentration data from plasma samples. The best base model, using the model building criteria, consisted of a two-compartment linear model with zero order input and exponential residual unknown variability. Other models could not be supported as they did not result in an improvement in objective function value or between-subject variability. Between-subject variability was included for all parameters except for non-EDD-f clearance (CL\textsubscript{NEDD-f}) for which it was considered to not be appropriate for inclusion because standard dialysis filters were used. A more mechanistic model contrasting dialysis clearance with different dialysis membrane characteristics was not explored as all patients received a standard dialysis dose with the same dialysers and membranes. A variance-covariance matrix was supported between clearance, central volume of distribution and peripheral volume of distribution. The model did not support between-occasion variability between any of the parameters. The final objective function for the base model was 131.853.

The covariates that described gentamicin clearance were patient lean body weight (normalized to 55kg) and the last plasma creatinine concentration before commencement of EDD-f. The addition of these parameters, reduced the objective function by 10.032 and 45.023 respectively (statistically significant change is 3.84 units). The covariate that described central volume of
distribution was total body weight normalized to 70kg. The addition of this parameter reduced the objective function by 4.925. The objective function for the final covariate model was 76.875. The final model for gentamicin clearance was represented by Equation 4:

\[
TVCL_{\text{NEDD-f}} = (\theta_1 \cdot \text{LBW}/55 \cdot \text{FCR}) \quad (3)
\]

\[
TVCL = TVCL_{\text{NEDD-f}} + TVCL_{\text{EDD-f}} \quad (4)
\]

where TVCL\text{NEDD-f} is the typical value of non-EDD-f clearance; LBW is lean body weight described by the equation from Janmahasatian et al(9) normalized to 55kg; FCR is the inverse of the final plasma creatinine concentration recorded in micromoles/L before commencement of EDD-f; and TVCL\text{NEDD-f} is the typical value of clearance during EDD-f. None of the other covariates statistically significantly improved the model and therefore could not be included.

The values of the parameters for the final model are given in Table 2. Table 2 presents the 95% confidence interval for the parameters computed from all bootstrap runs. The population value for clearance of gentamicin during EDD-f (CL\text{EDD-f}) was 2.54 L/hr (half-life (T\text{1/2}) 13.8hrs) compared with 0.23 L/hr (T\text{1/2} 153.4 hrs) when EDD-f was not being used (CL\text{NEDD-f}). The population value for volume of distribution was 0.55 L/kg.

Figure 1 displays the goodness of fit plots for the final model. The weighted residual graph shows no apparent visual or statistical bias for the prediction. Of the 265 samples included in the analysis, 10 samples had a concentration greater than 2 standard deviations outside that predicted by the model which we considered acceptable given the level of sickness severity and
likely pharmacokinetic heterogeneity of the patient cohort. It was noted that the model underpredicted the higher concentrations to a small extent. All subsequent dosing simulations were then based on this model. All other visual predictive checks were acceptable and confirmed the goodness of fit of the model. The plots show that the final pharmacokinetic model describes the measured gentamicin concentrations adequately when EDD-f is being used and when it is not being used.

\[\text{INSERT Figure 1}\]

\textbf{Dosing simulations}

Multiple dosing schedules were evaluated based on the final covariate model and assuming an MIC of 1mg/L. The ability for different dosing schedules to achieve pre-defined pharmacodynamic endpoints\(^{(4)}\) are described in Table 3. None of the simulated doses adequately achieved a target C\text{min} < 1.0mg/L with the best performed dosage being 3mg/kg infusion finishing at the time of EDD-f commencement achieving attainment in 29% of simulated patients. The maximal achievement of the AUC\(\text{0-24}\) (70-120mg.h/L) and C\text{max} (>10mg/L) pharmacodynamic targets for the simulated patients was by the 4mg/kg or 5mg/kg doses given either 30-minutes or one-hour before commencement of EDD-f.

Simulations performed on 48-hourly dosing achieved targets more successfully that 24-hourly dosing. We compared 96-hour duration of therapy of 5mg/kg 24-hourly with 6mg/kg 48-hourly. The median daily AUC\(\text{0-24}\) for 5mg/kg was 135.7mg.h/L (range 85.8 – 188.3mg.h/L) exceeded the recommended range (70-120mg.h/L) whereas the median AUC\(\text{0-24}\) for 6mg/kg 48-hourly dosing was more favourable at 88.7mg.h/L (range 48.4 – 122.0 mg.h/L). Both doses achieved a C\text{max} >10mg/L in 99.9% of simulated patients. Figure 2 describes the comparative simulated concentrations for the 5mg/kg 24-hourly regimen and the 6mg/kg 48-hourly regimen. This
figure shows the 6mg/kg 48-hourly schedule minimized the Cmin at 1.5mg/L compared with the 5mg/kg 24-hourly dosing value of 2.2mg/L.

Discussion

Knowledge of the significant clearance of gentamicin by EDD-f can be used to procure dosing regimens that will facilitate achievement of pharmacodynamic targets that are associated with optimal antibiotic activity and reduced potential for toxicity. Administration of gentamicin before commencement of EDD-f allows a high Cmax to be reached, then utilizes EDD-f for rapid drug clearance to minimize the Cmin and optimize the AUC$_{0-24}$. Specifically, in this study we have shown that administering 6mg/kg 48-hourly (for obese patients, we would recommend this dose be based on lean body weight) will ensure maximal achievement of AUC$_{0-24}$ and Cmax targets (4) in patients with EDD-f for infections caused by an MIC $\leq$1mg/L. It is likely that an organism with an MIC $> 2$mg/L cannot receive treatment in this scenario that will achieve the pharmacodynamic targets of Cmax:MIC, AUC$_{0-24}$:MIC or a low Cmin.

Using a 24-hour gentamicin dosing regimen with EDD-f does not appear to enable drug exposures that would be desired to minimize both nephro- and ototoxicity for critically ill patients with AKI. The simulations in this paper show that none of the simulated dosing regimens achieve a satisfactory Cmin ($<$1.0mg/L). Although the 3mg/kg regimens enable the highest proportion of simulated patients to achieve a Cmin $<$1.0mg/L, it is still only achieved in 29% of patients. This suggests that the clearance of gentamicin by EDD-f is not sufficient to reduce the likelihood of drug toxicity from once daily dosing. Extended interval dosing every 48-hours may be solution to this problem and the simulations performed in this study support use of 6mg/kg 48-hourly dosing to maximize achievement of Cmax targets (assuming an MIC $\leq$1mg/L).
The correct prescription of gentamicin during EDD-f is likely to be guided by the clinical scenario. Whilst daily 7mg/kg dosing achieves maximal bacterial kill pharmacodynamic targets, it risks toxicity, whereas dosing gentamicin at 6mg/kg 48-hourly achieves appropriate Cmax and AUC\textsubscript{0-24} targets with an improvement in Cmin targets as well. Smaller doses do not achieve Cmax or AUC\textsubscript{0-24} targets as proficiently as higher doses and only confer a small decrease in potential for gentamicin toxicity (target Cmin concentration). In the absence of achieving a target Cmin, minimizing the cumulative gentamicin exposure is the most appropriate method to ensure prevent toxicity. Pursuant to this, we would advocate short courses (≤4 days) of gentamicin be used where possible with 48-hourly 6mg/kg. The inherent pharmacokinetic variability observed in critically ill patients mandates that therapeutic drug monitoring still be undertaken to guide the timing of re-dosing after the administration of the first dose. Achievement of AUC\textsubscript{0-24} targets can then be facilitated by inputting two concentration-time points (pre-level and post-level) into freely available Bayesian dosing software such as TCI Works (Available at: [www.tciworks.info](http://www.tciworks.info)). Such an approach may enable more accurate dosing as well as the use of longer courses of therapy with decreased likelihood of toxicity.

The volume of distribution of gentamicin in this cohort of patients with AKI requiring EDD-f is largely similar to that observed in previous studies in critically ill patients without RRT requirements. The mean volume of distribution in our study was 0.55 L/kg which compares favourably with aminoglycoside data from Marik (0.41 L/kg)(12), Dasta et al (0.36 L/kg)(8) and Triginer (0.43 L/kg)(19). The incrementally higher volume of distribution of this cohort, compared with the result from previous studies, is likely to be due to the high level of sickness severity of the patients enrolled in this study.
There are some limitations with this study that we would like to declare. Firstly, due to the high volumes of dialysate generated by EDD-f, it was not possible to determine the concentration of gentamicin in the dialysate and therefore it was assumed that clearance during EDD-f is due solely to EDD-f. Secondly, our model was based on the homogenous EDD-f settings used in our intensive care unit and therefore, we are unable to extrapolate from this data the effect of different blood flow or ultrafiltrate flow rates. Thirdly, the simulations in this study assume that EDD-f continues for the planned 10-hour duration of RRT treatment. In patients, blood clotting on the filter frequently prevents this and therefore, therapeutic drug monitoring remains an essential part of re-dosing in such situations. Finally, the convenient sampling used in this study meant that this cohort had a high proportion of obese patients (5 patients were greater than 100kg) and 13 of the 14 patients were male. However, these anomalies were explained pharmacokinetically in our model by the inclusion of total body weight as a covariate of central volume of distribution. It is unlikely that clearance would be significantly affected by gender or obesity because the predominant clearance is caused by EDD-f.

**Conclusions**

Gentamicin remains an important antibiotic for use in critical care units, but is often withheld or inadequately dosed for fears of accumulation and toxicity in renal failure. When used in patients with AKI, EDD-f results in significant gentamicin clearance. In this paper, we have been able to show that, when dosed 48-hourly, a dose of 6mg/kg gentamicin, 30-minutes before the commencement of EDD-f, results in sufficient drug clearance to achieve pharmacodynamic targets associated with maximal bacterial killing. To achieve the optimal therapeutic effect of gentamicin, whilst minimizing toxicity, inputting pre-dose and post-dose therapeutic drug monitoring data into pharmacokinetic dosing software can be used to determine personalized dosing regimens for critically ill patients receiving EDD-f.
Acknowledgements

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Table 1 – Demographic and clinical details of enrolled patients. Group data are presented as median (interquartile range)

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<th>Age (years)</th>
<th>Sex</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Admission diagnosis</th>
<th>Ventilator duration (days)</th>
<th>ICU LOS (days)</th>
<th>APACHE III score</th>
<th>SOFA score</th>
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* ICU LOS – intensive care unit length of stay; APACHE – Acute Physiology and Chronic Health Evaluation; SOFA – Sequential Organ Failure Assessment; AAA – Abdominal aortic aneurysm
### Table 2 Bootstrap parameter final estimates of the final covariate model

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<th>Parameter</th>
<th>Mean</th>
<th>95% Confidence interval</th>
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<td>$CL_{NEDD-f}$ (L h$^{-1}$)</td>
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<td>Central volume of distribution</td>
<td>16.4</td>
<td>3.7</td>
</tr>
<tr>
<td>Intercompartmental clearance</td>
<td>20.5</td>
<td>57.7</td>
</tr>
<tr>
<td>Peripheral volume of distribution</td>
<td>110.5</td>
<td>9.1</td>
</tr>
<tr>
<td><strong>Random error</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residual unexplained variability (coefficient of variation%)</td>
<td>20.8</td>
<td>15.5</td>
</tr>
<tr>
<td>-------------------------------------------------------------</td>
<td>------</td>
<td>------</td>
</tr>
</tbody>
</table>

Key: $\text{CL}_{\text{EDD-I}}$ - clearance of gentamicin during EDD-I; $\text{CL}_{\text{NEDD-I}}$ clearance of gentamicin not due to EDD-I
Figure 1: Goodness of fit plots for the final pharmacokinetic model (a) population predicted concentrations (mg/L) versus weighted residuals; (b) individual predicted concentrations versus observed concentrations. The black dotted line is the line of linear regression $R^2 = 0.91$ and the grey unbroken line is the line of $x = y$. 
Figure 2: Simulation data for gentamicin administered (a) 5mg/kg 24-hourly (with EDD-f commencing daily 30-minutes post-dosing) and (b) 6mg/kg 48-hourly (with daily EDD-f). Simulations are presented as expected concentrations for the 5th, 50th and 95th percentile of simulated patients (n=1000).
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