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Determinants of gentamicin concentrations in critically ill patients: a population pharmacokinetic analysis

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ABSTRACT

When treating critically ill patients with gentamicin for severe infection, peak concentrations (C_{max}) determine clinical efficacy and trough concentrations (C_{min}) determine toxicity. Despite administration of body weight-standardised starting doses, a wide range of C_{max} is generally observed. Furthermore, in therapeutic drug monitoring, several measures of renal function are used to predict appropriate C_{min} and gentamicin dosing intervals, but the most accurate predictor is not known. This study aimed to quantify the impact of several patient parameters on gentamicin C_{max} values and to determine which measure of renal function best predicts gentamicin clearance (CL). Clinical data and serum gentamicin levels were retrospectively collected from all critically ill patients treated with gentamicin at our intensive care unit between 1 January and 30 June 2011. Data were analysed using non-linear mixed-effects modelling (NONMEM v.7.1.2). A two-compartmental model was developed based on 303 gentamicin concentration–time data from 44 critically ill patients. Serum albumin levels explained 25% of interindividual variability in the volume of distribution (V_d). Creatinine clearance calculated from the creatinine concentration in a 6-h urine portion ($CalcCL_{Cr}$) resulted in acceptable estimation of gentamicin CL, whilst serum creatinine (SCr) and creatinine clearance estimated by the Cockcroft–Gault formula ($CGCL_{Cr}$) overestimated gentamicin CL and therefore underestimated C_{min}. In conclusion, low albumin concentrations resulted in a larger V_d and lower C_{max} of gentamicin. These results suggest that use of a higher gentamicin starting dose in critically ill patients with hypoalbuminaemia may prevent underdosing. Urinary $CalcCL_{Cr}$ is a better predictor of C_{min} than SCr or $CGCL_{Cr}$.

1. Introduction

In the treatment of sepsis in critically ill patients, early and appropriate antibiotic therapy has been shown to have a greater impact on survival than any other intervention [1–3]. Therefore, adequate dosing of antibiotics is of paramount importance in these patients. Gentamicin is often included in empirical treatment regimens for sepsis, with dosing schedules aimed at obtaining a ratio of peak concentration over minimum inhibitory concentration (C_{max}/MIC) of >10 for optimal clinical efficacy [4,5]. According to Dutch guidelines on therapeutic drug monitoring (TDM), a C_{max} of 15–20 mg/L is considered to be therapeutic [6]. However, an evidence-based strategy for selecting optimal gentamicin starting doses to achieve this target in critically ill patients has not been established [7]. Body weight-standardised starting doses result in a wide range of C_{max}, indicating large interindividual variability (IIV) in this patient group [8–10]. Depending on the MIC of the causative micro-organism, the likelihood of achieving C_{max}/MIC >10 when using a starting dose of 5 mg/kg ranges from only 27.3% for an *Escherichia coli* strain with an MIC_{90} of 1 mg/L to 0% for a *Pseudomonas aeruginosa* strain with an MIC_{90} of 4 mg/L [8]. IIV in C_{max} is largely caused by variability in the volume of distribution (V_d) of gentamicin in critically ill patients, which is reported to range from 16% to 64% [8,11,12]. This variability in V_d is partially determined by body weight [11], the severity of disease [13], administration of total parenteral nutrition (TPN) [14] and several other determinants that are correlated to a certain extent with the capillary leak syndrome that occurs during sepsis [15]. However, the contribution to variability in V_d of each separate determinant is unknown at present.

Whilst a high gentamicin C_{max} is associated with efficacy, a high trough level (C_{min}) is associated with toxicity, hence TDM is indicated to minimise the risk of nephrotoxicity [16,17]. According to Dutch guidelines, a C_{min} of <1.0 mg/L should be aimed for. Gentamicin C_{min} is strongly associated with renal function, and measures

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of renal function, such as serum creatinine (SCr), total daily diuresis and creatinine clearance estimated according to the Cockcroft–Gault equation or calculated from a urine portion, are widely used to predict appropriate dosing intervals, with [18] or without [19] the use of a pharmacokinetic (PK) model. In critically ill patients, however, these measures of renal function are known to poorly predict actual renal function [20] and may lead to poor prediction of C_{min}.

In this study, a population PK model for gentamicin in critically ill patients was developed to identify which parameters explain the IIV in V_d and to quantify the impact of these parameters on C_{max}. Moreover, the measure of renal function that best predicts gentamicin clearance (CL) and thus C_{min} was investigated. Such knowledge is essential for optimising gentamicin dosing schedules in critically ill patients, thereby maximising efficacy and minimising toxicity.

2. Materials and methods

2.1. Patients and data

These retrospective analyses were performed using clinical data and serum gentamicin levels obtained as part of routine clinical care in critically ill patients admitted to the intensive care unit (ICU) of the Academic Medical Center in Amsterdam (The Netherlands). Data from all patients treated with gentamicin between 1 January and 30 June 2011 were included. According to Dutch law on medical research (WMO, article 1), no ethical approval is required when using anonymous data from routine diagnostic databases, as was done for the data analysed in this study. Routine clinical care at our institution includes measurement of gentamicin C_{max} drawn within 1 h after infusion of the first dose, which is infused over 30 min. To determine the half-life, a second sample is collected the next morning at 06:00 h, regardless of the time the first dose was administered. Subsequently, gentamicin concentrations are routinely measured three times a week while on treatment in order to monitor C_{min} and to adjust the dosing interval according to Dutch TDM guidelines [6]. The starting dose during the study period was 4 mg/kg total body weight (TBW), except for patients treated for endocarditis due to Gram-positive micro-organisms, who were treated with 3 mg/kg for synergistic effect in combination with a cell-wall-targeting antibiotic.

The following data were retrieved from the electronic Patient Data Monitoring System (PDMS): dose and timing of gentamicin; age; sex; TBW, ideal body weight (IBW) [21] and adjusted body weight (ABW) [22]; height; and severity of disease as assessed by the Acute Physiology and Chronic Health Evaluation (APACHE) II score [23]. During therapy, daily SCr, urinary creatinine concentration in a 6-h urine portion (00:00–06:00 h), daily diuresis and fluid balance, daily albumin level, administration of TPN, and application of continuous venovenous haemofiltration (CVVH) were noted. Both daily and total fluid balance were automatically calculated from data in the PDMS, in which all intravenous and oral input of fluids as well as all urine and non-urine outputs were monitored every hour in the PDMS. Creatinine clearance was estimated according to the Cockcroft–Gault equation ($CGCL_{Cr}$) [24] and was calculated from a 6-h urine portion by the formula $\{CalcCL_{Cr} = [creatinine_{urine}\ (mg/dL)/creatinine_{serum}\ (mg/dL)] \times [(volume_{urine}\ (mL)/(time\ (h) \times 60]\}$. CVVH was performed using a NxStage System One Cycler (NxStage Medical Inc., Lawrence, MA) and a high-flux polysulfone dialyser (FX80 CorDiax; Fresenius Medical Care, Bad Homburg, Germany) with a 1.8 m^2 surface. The blood flow rate was 150–180 mL/min and replacement fluid was infused by post-dilution at 35 mL/kg/h. The flow rate of ultrafiltrate during CVVH was calculated as:

$$\text{Flow rate of ultrafiltrate} = [(F_{subst} \times t_{di}) + UF_{vol}]/t_{di} \quad (1)$$

where F_{subst} is the flow rate of the replacement fluid, t_{di} is the time (h) within the dosing interval during which CVVH was applied, and UF_{vol} is the net ultrafiltrate volume (L) within the dosing interval.

Gentamicin concentrations were measured using fluorescence polarisation immunoassay (FPIA) technology on an AxSYM System (Abbott Diagnostics, Abbott Park, IL). The limit of detection was 0.49 mg/L. Accuracy at concentrations of 1, 4 and 8 mg/L was 108.2%, 110.7% and 106.9%, respectively. Intraday precision at concentrations of 1, 4 and 8 mg/L was 6.1%, 2.9% and 4.9%, respectively, and interday precision at these concentrations was 5.9%, 4.6% and 5.0%, respectively.

2.2. Population pharmacokinetic data analysis

Gentamicin concentration–time data were analysed using non-linear mixed-effects modelling (NONMEM v.7.1.2; Icon Development Solutions, Ellicott City, MD) [25]. A three-step approach was undertaken during the modelling process.

During the first step, a compartmental population PK model was developed, quantifying gentamicin V_d and CL. For models with two or more compartments, these parameters were central and peripheral volume(s) of distribution (V_1, V_2, V_3, etc.) and CL and intercompartmental clearance (Q_1, Q_2, etc.). Moreover, IIV was estimated in the PK parameters assuming a log-normal distribution. In addition, interoccasion variability (IOV) was estimated since the pharmacokinetics of gentamicin in a critically ill patient can vary substantially over time [26]. Residual variability was estimated by testing additive, proportional and combined error models. TBW, IBW and ABW were tested as a covariate for allometric scaling. Since IBW resulted in the best fit, PK parameters were allometrically scaled to 70 kg IBW [21,22,27]. The effect of CVVH was taken into account as shown in Eq. (2), not only allowing an estimation of different values for CL in an individual patient (CL_i) on or off CVVH, but also allowing the estimation of IIV in CL when on CVVH (CL_{CVVH}) and when off CVVH (CL_{noCVVH}):

$$\begin{aligned} &\text{Off CVVH} \quad CL_{ij} = \theta_{noCVVH} \times (IBW_i/70)^{0.75} \times \exp(\eta_{noCVVHi} + \kappa_{noCVVHj}) \\ &\text{On CVVH} \quad CL_i = \theta_{CVVH} \times (IBW_i/70)^{0.75} \times \exp(\eta_{CVVHi}) \end{aligned} \quad (2)$$

where $CLij$ is the gentamicin CL for individual i on occasion j, θ_{noCVVH} and θ_{CVVH} are population values for CL when off and on CVVH, respectively, $\eta_{noCVVHi}$ and η_{CVVHi} are estimates of IIV in CL when off and on CVVH, respectively, both with mean 0 and variance ω^2, and $\kappa_{noCVVHj}$ is the estimate for IOV in CL when off CVVH with mean 0 and variance π^2 [26].

During the second step, different covariates other than IBW and CVVH were tested for their correlation with gentamicin V_d (V_1 and/or V_2) and CL. First, the following variables were tested using univariate analysis: age; sex; height; SCr; $CGCL_{Cr}$; $CalcCL_{Cr}$; total daily diuresis, fluid balance of the concerning day; fluid balance since ICU admittance; albumin level; APACHE II score; administration of TPN; and flow rate of ultrafiltrate during CVVH. If covariate data were not available from the same day that the sample was drawn for gentamicin concentration measurement, they were considered missing. Handling of missing covariate data was done in such a way that concentration–time data from patients for whom covariate data were missing were ignored in estimating the correlation between PK parameter and covariate, as described previously [28]. This yielded estimation of a missing-data parameter for every covariate effect. When renal function was evaluated as a covariate on gentamicin CL, SCr, $CGCL_{Cr}$ and $CalcCL_{Cr}$ values were ignored (counted as missing) when a patient received CVVH in the preceding week, as SCr (which