Empirical models for dosage optimization of four β-lactams in critically ill septic patients based on therapeutic drug monitoring of amikacin

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A R T I C L E   I N F O

Article history:
Received 18 September 2009
Received in revised form 27 November 2009
Accepted 8 December 2009
Available online 28 December 2009

Keywords:
Amikacin
β-lactams
Sepsis
Pharmacokinetics
Multivariate analysis
Therapeutic drug monitoring

A B S T R A C T

Objectives: The study aims to develop empirical models able to predict the pharmacokinetics (PK) of four β-lactams using the amikacin (AMK) therapeutic drug monitoring (TDM), in order to optimize their dosage regimens.

Design and methods: 69 critically ill septic patients were included. All received a first dose of AMK combined with piperacillin/tazobactam, ceftazidime, cefepime or meropenem. A multivariate analysis was performed to predict the β-lactam PK using AMK PK parameters estimated from TDM and using pathophysiological variables.

Results: An optimal prediction model was identified for each PK parameter of each β-lactam. The best predictor of each model was one of the AMK PK parameters estimated from TDM. Other variables included colloid solution, renal and hepatic biomarkers, age and body weight.

Conclusion: PK of the four β-lactams could be easily and rapidly predicted in critically ill septic patients using the AMK TDM. These predictions could improve the β-lactam dosages in clinical practice.

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Introduction

Mortality rates in intensive care unit (ICU) patients with severe sepsis or septic shock remain unacceptably high, reaching 30% to 50% [1–4]. Prompt initiation of the right antibiotic therapy is the cornerstone to maximize the successful outcome of treatment in critically ill patients [5–10], and there is evidence over the last decade that the optimal antibiotic dosage regimen is at least as important [11–14]. The individual optimization of the antibiotic dosages should ideally involve both pharmacokinetic (PK) and pharmacodynamic (PD) parameters, the so-called efficacy indices [15,16].

During severe sepsis or septic shock, there are two important PK modifications, i.e. an increase in volume of distribution (Vd), due to leaky capillaries and decreased protein binding, and a reduction in total body clearance (CL), associated with renal and/or hepatic dysfunction [17–22]. Regrettably, in severely septic patients, the antibiotic dosage regimens are often based on PK data obtained in healthy volunteers or non-critically Ill patients, without consideration for the sepsis-induced PK changes, particularly critical at the onset of the treatment (first 24 h). This may result in inadequate drug concentrations and consequently affect the outcome of patients. Moreover, large interindividual PK variations have been reported in critically ill patients, making empirical fixed dose strategy difficult because of the unpredictability of drug concentrations [23]. Individual optimization of the antibiotic dosage regimens needs therefore to be considered for patients with severe sepsis, reinforcing the role of therapeutic drug monitoring (TDM).

Antibiotic therapy in critically ill septic patients usually consists of an aminoglycoside combined with a broad-spectrum β-lactam [24]. In clinical practice, the aminoglycoside dosage regimens are routinely adjusted by serum concentration monitoring. Among PK-based dosing methods dedicated to aminoglycoside TDM, the non-Bayesian least-squares method has the advantage to not require knowledge of the PK parameter distribution in the population [25,26]. Initially described by Sawchuk and Zaske [27,28] this approach is applicable when the PK can be adequately described by a one-compartment model with first-
order elimination and when it is required to maintain drug concentrations within a desired range. Individual PK parameters can be obtained from at least two blood samples drawn during the elimination phase. Using the appropriate efficacy index, they are then used to estimate the optimal patient dosage regimen.

Unlike aminoglycosides, β-lactam dosage regimens are frequently inferred and roughly adapted only from the patient’s pathophysiological status. The lack of TDM for these antibiotics may limit their clinical use optimization. However, due to chemophysical and PK similarities between aminoglycosides and β-lactams (i.e. hydrophilicity, low molecular weight, low Vd, renal elimination, low plasma protein binding) [18], knowledge of aminoglycoside PK obtained from TDM could be used to predict β-lactam PK parameters, allowing therefore individualized dosage adjustment in a cost-effective strategy, without additional blood sampling.

Since amikacin (AMK) is largely used in Europe, the objectives of the study are: (i) to describe the first dosing PK of AMK and four β-lactams (piperacillin/tazobactam (PIP/TAZ), ceftazidime (CAZ), cefepime (FEP) and meropenem (MEM)) in critically ill septic ICU patients, from serum concentrations obtained after full validation of their analytical methods, and (ii) to develop empirical models able to predict the β-lactam PK from AMK TDM and from variables such as demographic data (age, weight, ...) routine biochemistry markers (creatinine, albumin, ...) and blood cells counting. The choice of β-lactam empirical treatment is based on the clinical recommendations for nosocomial infections in Belgium (e.g. MEM is preferred to imipenem due to its lower toxicity) [29].

Methods

Study design, patients, antibiotic treatment and data collection

The open-labeled, observational, clinical study was conducted between January 2005 and April 2007 in the ICU of four Belgian university hospitals (Cliniques Universitaires St-Luc, Erasme Hospital and Universitair Ziekenhuis Brussel in Brussels, and St-Pierre Hospital in Ottignies) after approval by the respective Ethics Committees. Before enrollment, written consent was obtained from patients or their legal representatives.

Eligible patients were diagnosed with severe sepsis or septic shock at their ICU admission or during their ICU stay. Severe sepsis and septic shock were defined according to standard criteria [30]. Patients meeting one of the following criteria were excluded: (i) age <18 years or >90 years, (ii) pregnancy or lactation, (iii) previous administration of any of the investigated antibiotics during the week before inclusion, (iv) chronic renal failure requiring dialysis and (v) allergy to any of the investigated drugs. The study period was limited to the first 24 h of antibiotic therapy, considered as the most critical period.

All patients were treated with a first dose of AMK (25 mg/kg) combined with one of the four following broad-spectrum β-lactams: PIP/TAZ (4 g/500 mg), CAZ (2 g), FEP (2 g) or MEM (1 g) selected according to the local clinical practice. Further β-lactam administration was based on standard dosage regimens and adapted to renal function: 4 g/500 mg of PIP/TAZ every 6 h, 2 g of CAZ, 2 g of FEP and 1 g of MEM every 8 h. Next doses of AMK were determined according to TDM. The antibiotic combination was given by two separate intravenous lines as a 30-min infusion. 3-ml blood samples were collected without anticoagulant immediately before and at 1, 1.5, 4.5, 6 or 8, and 24 h after onset of the first infusion; these blood collection time points are supposed to belong to the elimination phase of all five antibiotics. The exact sampling time was recorded by the nursing or medical staff. Blood samples were centrifuged at 4000×g for 10 min at 4 °C after blood clotting. Taking into account the possible drug instability at room temperature, serum samples were stored at −70 °C until shipment in dry ice to a reference laboratory for analysis.

For each patient, demographic and biometric data, complete blood count and routine biochemistry markers were recorded at the baseline (i.e. before start of antibiotic therapy). Similarly, the Acute Physiology And Chronic Health Evaluation (APACHE) II and Sepsis-related Organ Failure Assessment (SOFA) scores were determined [31,32]. Infused volumes of resuscitation fluids (crystalloid and colloid solutions) were also recorded in the database.

Reagents, sample preparation and analytical methods

All antibiotic quantitative analyses were centralized in a reference laboratory.

Reagents

Calibrations were performed using each drug generously provided by Wyeth Pharmaceuticals, Madison, NJ, USA, for piperacillin; GlaxoSmithKline Pharmaceuticals,Genval, Belgium, for ceftazidime; Bristol-Myers Squibb, NY, USA, for cefepime; and AstraZeneca, London, UK, for meropenem. Visnadine and cefazolin, used as internal standard, were obtained from Indena (Milan, Italy) and Sandoz (Holzkirchen, Germany), respectively. Acetonitrile HPLC-grade and triethylammonium phosphate buffer solution (1 M, pH 3) were purchased from Sigma-Aldrich (Munich, Germany), and sodium 1-octanesulfonate monohydrate from Acros Organics (Geel, Belgium). Sulfuric acid and all the chemicals used for protein precipitation and extraction were supplied by Merck (Darmstadt, Germany). Ultrapure water was obtained from a MilliQ® UF-Plus apparatus (Millipore Corp, Bedford, MA, USA).

Analytical method for amikacin

The AMK serum concentrations were quantified by Fluorescence Polarization ImmunoAssay (FPIA) using the TDx analyzer (Abbott Laboratories, Abbott Park, IL, USA) [33,34], according to the manufacturer recommendation, with a limit of quantification (LOQ) of 0.8 μg/mL.

Sample preparation and analytical methods for β-lactams

The β-lactam concentrations were determined by High Performance Liquid Chromatography (HPLC) with Diode Array Detection (DAD). The antibiotics were diluted in water in order to reach stock solution aliquots of 1 mg/mL, stored at −20 °C. Before each assay, a fresh calibration curve was prepared from the stock solution and blank serum, at the following concentrations: 0.75, 1, 2, 5, 10, 25 and 50 μg/mL for PIP; 5, 10, 25, 50 and 100 μg/mL for CAZ; 0.1, 0.25, 0.5, 1, 5, 10, 25 and 50 μg/mL for FEP or MEM. The liquid-liquid extraction procedures and chromatographic conditions are described below.

PIP. 400 μL of serum sample and 200 μL of IS solution (visnadine 50 μg/mL in acetonitrile) were added in a 5-ml glass tube and vortex-mixed for 15 s before a 10-min incubation at 4 °C. 50 μL of an aqueous solution of perchloric acid 15% (w/v) and 50 μL of an aqueous solution of sodium tungstate 25% (w/v) were then sequentially added, followed by vortex-mixing. The tube was then incubated at 4 °C for 10 min and centrifuged at 4000×g for 7 min. 100 μL of the supernatant were transferred in an injection vial. Analyses were performed using a HPLC HP1090 Series II, coupled to a DAD (Hewlett Packard, Palo Alto, CA, USA). 20 μL were injected on a LiChroCART Superspher® 100 RP-18 endcapped column (125×4 mm ID, 5 μm particle size) (Merck, Darmstadt, Germany), equipped with a pre-column (4×4 mm ID, C-18) and maintained at 40 °C. The mobile phase, consisting of solvent A (25 mM triethylammonium phosphate buffer solution, pH 3) and solvent B (acetonitrile), was delivered at a flow rate of 1 mL/min according to the following gradient: 0 min, 85/15%; 10 min, 60/40%;
13.5 min, 30/70%; 17.5 min, 0/100%, for solvents A/B respectively. The 230- and 320-nm bands were used to detect PIP and its IS (visnadine), respectively, during a 18 min run-time.

CAZ. The extraction procedure was similar to the one used for PIP. 50 μL of the IS solution (cefazolin 1 mg/mL in water) were added to 400 μL of serum sample together with 200 μL of acetonitrile in a 5-mL

Fig. 1. Adapted HPLC chromatogram from 4 chromatograms obtained from plasma spiked with 10 μg/mL of each analyte. ① cefepime (time of retention: 1.72 min, wavelength: 254 nm); ② ceftazidime (time of retention: 2.10 min, wavelength: 254 nm); ③ meropenem (time of retention: 2.29 min, wavelength: 320 nm); ④ cefazolin (internal standard at 1 mg/mL, time of retention: 7.20 min, wavelength: 254 nm); ⑤ piperacillin (time of retention: 7.69 min, wavelength: 230 nm); ⑥ visnadine (internal standard at 50 μg/mL, time of retention: 15.63 min, wavelength: 320 nm).

Fig. 2. HPLC chromatograms of (A) a plasma blank, and (B) a plasma sample from a patient treated with ceftazidime (52 μg/mL). The internal standard (cefazolin 1 mg/mL) was added to both samples.
glass tube. Analyses were performed on a HPLC Waters Alliance 2795 Separation Module, coupled to a PhotoDiode Array detector (Waters, Milford, MA, USA). 20 μL were injected on an Ultrasphere® ODS column (250 × 4.6 mm ID, 5 μm particle size) (Beckman Coulter, Fullerton, CA, USA), maintained at 40 °C. The mobile phase was isocratically delivered at a flow rate of 1 mL/min and consisted of 88% 25 mM triethylammonium phosphate buffer solution (pH 3) and 12% acetonitrile. The 254-nm band was used to detect both CAZ and its IS (cefazolin), in a 9 min run-time.

To a 500 μL of serum sample, 10 μL of IS solution (MEM 1 mg/mL in water) and 750 μL of acetonitrile were added in a 5-mL glass tube and vortex-mixed for 1 min before a 45-min incubation at 4 °C. After appropriate centrifugation (4000×g, 7 min), 950 μL of supernatant were transferred to a second 5-mL glass tube, centrifuged at 4000×g for 7 min. 800 μL of the resulting supernatant were further transferred together with 3 mL of dichloromethane in a third 5-mL glass tube, vortex-mixed for 1 min and centrifuged at 4000×g for 7 min. Finally, 100 μL of the supernatant were transferred in a HPLC injection vial. Analyses were performed using a HPLC HP 1090 Series II, coupled to a DAD. 5 μL were injected on the same pre-column and analytical column as described for PIP. The mobile phase was isocratically delivered at a flow rate of 1 mL/min and consisted of 79% 5 mM sodium 1-octanesulfonate monohydrate (adjusted to pH 3 with 2.5 M sulphuric acid) and 21% acetonitrile. The 254- and 320-nm bands were used to detect FEP and its IS (MEM), respectively. The run-time was 4 min.

MEM. The extraction procedure, the apparatus and the chromatographic conditions were identical to those used for FEP, except for the IS solution (50 μL of FEP 1 mg/mL in water) and the wavelength bands (320-nm to detect both MEM and FEP).

All methods were validated according to the published acceptance criteria for specificity, linearity, accuracy, precision (intra-day (repeatability), inter-day (intermediate precision)) and sensitivity (LOD (limit of detection) and LOQ) [35,36]. The specificity was investigated for possible interference with a number of drugs commonly administered in the ICU (sedatives (midazolam, propofol, ketamine), analgesics (morphine, remifentanil, fentanyl), insulin, antibiotics (vancomycin), antipyretics, antacids), by analysing serum samples collected before the antibiotic infusion. In addition, the carry-over effect was tested.

Pharmacokinetic analysis

PK of the five investigated antibiotics was individually assessed using WinNonlin® Professional version 5.0.1. software (Pharsight Corporation, Mountain View, CA, USA). Due to the absence of sampling in the distribution phase, a one-compartment model with first-order elimination was selected to fit data. Investigated PK parameters included maximal serum concentration (Cmax), Vd, CL, elimination half-life (t1/2) and area under the serum concentration-time curve (AUC). Vd and CL were normalized to the body weight.

AMK PK parameters were further obtained using PharMonitor [37], a TDM software based on the Sawchuk–Zaske method, from serum concentrations determined 1 h and 6 or 8 h after the start of the antibiotic infusion.
infusion. These time-points have been selected after testing different combinations.

**Statistical analysis**

The performance of PharMonitor to adequately generate the AMK PK parameters of each patient was first assessed using the relative mean prediction error (MPE [%]) (Eq. 1) and the relative root mean square prediction error (RMSE [%]) (Eq. 2) [38]. MPE measures the magnitude of the systematic component of the prediction error (PE); the smaller the absolute MPE value, the smaller will be the bias of the prediction. RMSE measures the standard deviation of the prediction error; the smaller the RMSE value, the greater will be the precision of the prediction.

\[
\text{MPE} [%] = \frac{1}{N} \sum_{i=1}^{N} \left( \frac{\text{Value}_{\text{pred}} - \text{Value}_{\text{ref}}}{\text{Value}_{\text{ref}}} \right) \times 100 \\
= \frac{1}{N} \sum_{i=1}^{N} \text{PE}_i [%]
\]

\[
\text{RMSE} [%] = \sqrt{\frac{1}{N} \sum_{i=1}^{N} \text{PE}_i^2 [%]}
\]

The AMK PK parameters obtained from PharMonitor were considered in the calculation of MPE and RMSE as predicted values (Value pred), and those obtained from WinNonlin as reference values (Value ref).

In a second step, a multiple linear regression analysis was performed in order to predict Vd, CL, and AUC of each β-lactam. The following variables were tested: PharMonitor AMK PK parameters, demographic and biometric data (sex, age, body weight), renal function markers (creatinine, urea, potassium, glomerular filtration rate estimated either from the Cockcroft and Gault formula [39], or from the simplified Modification of Diet in Renal Disease formula (MDRD) [40]), hepatic function markers (albumin, total protein, total bilirubin), sparteine and aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, alkaline phosphatase, prothrombin time, activated partial thromboplastin time, plasma total protein, and infused volumes of resuscitation fluids (crystalloid and colloid solutions). The multivariate analysis was carried out by testing different data transformations, such as original versus log-transformed data, original versus categorized data, and PK parameters (Vd, CL and AUC) with or without normalization to body weight. The prediction models were built using a stepwise selection of significant variables using both the forward inclusion and the backward exclusion [41]. To limit the propagation error, the maximal number of variables included in the final model was three. The sensitivity of developed models to outliers was assessed by computing the distribution of residuals and the Cook’s influence, and by performing a jack-knife analysis [42]. For each β-lactam PK parameter, the best model was selected using the two predictive performance indices: MPE [%] and RMSE [%] [38]. The β-lactam PK parameters obtained from WinNonlin were investigated in the calculation of these indices as reference values. A third performance criterion was considered, i.e. the percentage of patients with clinically unsatisfactory RPE’s, fixed at ≥ 20% / ≥ 30% / 40% and 40% / 40% / 40%.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Prediction models of the β-lactam Vd, CL, and AUC.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multiple linear regression equations</strong></td>
<td><strong>r²</strong></td>
</tr>
<tr>
<td>PIP Vd = 0.5000 – 0.0030 AMK C max + 0.1000 Cd</td>
<td>0.58</td>
</tr>
<tr>
<td>CAZ Vd = 1.6030 × (AMK Vd) 1.1788</td>
<td>0.84</td>
</tr>
<tr>
<td>FEP Vd = 0.4983 – 0.0022 AMK C max + 0.0525 Cd</td>
<td>0.76</td>
</tr>
<tr>
<td>MEM Vd = 0.4112 – 0.0019 AMK C max + 0.1532 Cd</td>
<td>0.56</td>
</tr>
<tr>
<td>PIP CL = 23.4420 × (AMK CL) 0.7724 × (Ur) 0.1845 × (aPTT) 0.04345</td>
<td>0.90</td>
</tr>
<tr>
<td>CAZ CL = 24.7237 × (AMK CL) 0.9146 × (Ur) 0.3466 × (K) 0.0109</td>
<td>0.89</td>
</tr>
<tr>
<td>FEP CL = 3.5000 × (AMK CL) 0.5673 × (Ur) 0.1789</td>
<td>0.71</td>
</tr>
<tr>
<td>MEM CL = 0.8466 × (AMK CL) 0.5404 × (Prottot) 0.6196</td>
<td>0.85</td>
</tr>
<tr>
<td>PIP AUC = 2.0285 × (AMK AUC) 0.8002 × (aPTT) 0.2523 × 0.4967</td>
<td>0.94</td>
</tr>
<tr>
<td>CAZ AUC = 0.3738 × (AMK AUC) 1.3205 × 0.8086</td>
<td>0.90</td>
</tr>
<tr>
<td>FEP AUC = 3.1356 × (AMK AUC) 1.8132 × 0.5828</td>
<td>0.90</td>
</tr>
<tr>
<td>MEM AUC = 2.3357 × (AMK AUC) 0.0009 × 1.6607 × 0.8238</td>
<td>0.92</td>
</tr>
</tbody>
</table>

Pip, piperacillin; CAZ, ceftazidime; FEP, cefepime; MEM, meropenem; AMK, amikacin; C max, maximal serum concentration; Vd, volume of distribution; CL, total clearance; t1/2, elimination half-life; AUC, area under the serum concentration-time curve.
The statistical analyses were performed using JMP Statistical Discovery™ 6.0.0. software (SAS Institute Inc., Cary, NC, USA). All PK values were expressed as median and range. *P*-values <0.05 were considered to be statistically significant.

**Results**

Under the chromatographic conditions described above, PIP, CAZ, CEF, MER and their respective IS were identified by sharp and well resolved peaks (Figs. 1 and 2). No interference was identified in the analytical methods, either by endogenous compounds or by co-administered drugs as described above. The linearity was statistically confirmed over the concentration range tested for each β-lactam and was associated with $r^2 >0.999$. The four analytical methods were accurate and precise. LOD and LOQ respectively were 0.50 and 0.75 μg/mL for PIP, 2.00 and 5.00 μg/mL for CAZ, 0.07 and 0.10 μg/mL for FEP and MEM. The methods did not display any carry-over. Appropriate dilution was performed for clinical samples with concentrations above the upper analytical range.

The study included 69 adult patients (44 men) with severe sepsis ($n=17$) or septic shock ($n=52$), with a median age of 65 years (range 22–89 years) and a median weight of 70 kg (range 38–120 kg). At the onset of the antibiotic therapy, median APACHE II and SOFA scores were 20 (range 6–45) and 8 (range 1–19), respectively. Blood cultures were positive in 68% of patients; Gram-negative bacteria were the most frequent isolated micro-organisms (41%).

A total of 20 PK profiles were completed for PIP, 17 for CAZ, 17 for FEP, 15 for MEM and 69 for AMK; they are illustrated in Figs. 3–7, respectively. The corresponding median PK parameters are presented in Table 1. Antibiotic serum concentrations and PK parameters were characterized by a large variability.

When assessing the PharMonitor performance to adequately estimate AMK PK from serum concentrations determined 1 h and 6 or 8 h after onset of the infusion, the following MPE [%] and RMSE [%] were respectively reported: −5.25% and 5.57% for $C_{max}$; 4.71% and 5.43% for Vd; −4.18% and 19.88% for CL; 5.31% and 18.07% for $t_{1/2}$; 1.08% and 15.98% for AUC.

The best models predicting Vd, CL and AUC of the four β-lactams are listed in Table 2 with their respective $r^2$, and are illustrated in Figs. 8–10, respectively. For each model, no outlier in the population dataset and patient influencing covariate selection was identified: residuals were normally distributed, and the Cook's influence and jack-knife analysis gave satisfactory results (Cook's distances <1 and CV <5%, respectively). β-lactam Vd and CL were better predicted when normalized to body weight. AMK $C_{max}$ and colloid solution for fluid resuscitation were retained as significant predictive variables of β-lactam Vd, except for CAZ. Elimination of PIP, CAZ and FEP was influenced by both AMK CL and renal biomarker(s) (i.e. urea, potassium). Moreover, hepatic biomarkers (i.e. activated partial thromboplastin time, total protein) were found to significantly affect PIP and MEM CL. Age was retained as a significant predictive variable of MEM CL and AUC. Based on the inclusion and exclusion probabilities, AMK PK parameters appeared the best predictors in all models. Table 3 displays the predictive performance of each developed model.

**Discussion**

In the present study, PK of AMK and four β-lactams (PTZ, CAZ, FEP and MEM) have been characterized in 69 patients with severe sepsis or septic shock, following the first dose of antibiotics, considering the
first 24 h as a particularly important period in the management of these patients. This is the first report proposing empirical models for dosage optimization of four \( \beta \)-lactams based on AMK concentration monitoring. These models have been validated using reliable statistical tools: distribution of residuals, Cook’s influence, jack-knife analysis [42], and predictive performance parameters as suggested by Sheiner and Beal [38]. The main advantage of these models predicting the \( \beta \)-lactam PK is the ease of their use in clinical practice; while predictive biometric variables are easily available, predictive AMK PK and biochemistry parameters are rapidly measured and can be obtained from the same blood sample. In a recent paper, Panomvana et al. [43] have explored the association between the PK of AMK and CAZ. They have proposed bivariate equations allowing prediction of the PK parameters. Although their models give clinicians helpful guidance in adjusting the dosage regimens of AMK and CAZ, a careful statistical validation should be required to assess sensitivity and predictive performance of their equations.

Severe sepsis is known to affect drug disposition, as a consequence of alterations in capillary permeability, protein binding and organ function [17–22]. Although it is established that free drug fraction is related to the pharmacological effect [44–46], only total concentrations have been measured in this study. Indeed, protein binding of the five investigated antibiotics is low (0–11% for AMK, 21% for PIP, ±10% for CAZ, <16.4% for FEP, ±2% for MEM) [47], and any change in free fraction is not expected to cause significant impact in therapeutic efficacy [48]. The present study has confirmed the sepsis-induced PK modifications; when compared to healthy subject values, \( V_d \) and \( t_{1/2} \) were increased, and \( \text{CL} \) was reduced [49,50]. In addition, an important interindividual PK variability has been observed, highlighting therefore the need for TDM to individually adjust the antibiotic dosage regimens (Fig. 3–7, Table 1).

The Sawchuk–Zaske method is a practical TDM approach; it only requires two blood sampling during the elimination phase to adequately estimate the individual patient PK parameters [27,28]. Moreover, it has been widely used and validated in various populations, including patients with extreme PK parameter values [27,51–53]. Its robustness and independency from population PK knowledge make this approach very attractive for ICU patients with severe sepsis or septic shock. Satisfactory accuracy and precision (i.e. MPE and RMSE, respectively) have been obtained when investigating the performance of this method to adequately assess the AMK PK forecasting. Unlike aminoglycosides, \( \beta \)-lactam concentration monitoring is difficult to implement in clinical practice for analytical and economical reasons [54]. The development of models able to predict \( \beta \)-lactam PK from AMK TDM, by performing a multivariate analysis, could therefore be of clinical interest.

From the multivariate analysis, PIP, FEP and MEM \( V_d \) were found to be negatively associated with AMK \( C_{\text{max}} \) and positively associated with fluid resuscitation volume (infused colloid solution). Fluid resuscitation aims to restore circulating intravascular volume (lost due to vasodilatation, venous pooling and capillary leakage), haemodynamic stability and organ perfusion. The infused colloid volume contributes to increase the intravascular volume but may affect drug concentrations by dilution. Antibiotic PK is therefore not only affected by pathophysiological status but also by associated treatments. Unlike other \( \beta \)-lactams, CAZ \( V_d \) has been directly associated with AMK \( V_d \). This could be explained by the similar physicochemical properties of both drugs; they are soluble in water and have equivalent molecular weights (585.6 g/mol for AMK, 546.6 g/mol for CAZ). The observed association between hepatic (activated partial thromboplastin time and total protein) and renal

![Fig. 9. Observed versus predicted total clearance (CL) of (A) piperacillin, (B) ceftazidime, (C) cefepime and (D) meropenem in critically ill septic patients.](image-url)
(urea and potassium) biomarkers, retained as variables, and antibiotic CL could be explained by the drug elimination route(s). Indeed, while PIP and MEM are known to be eliminated both via renal and hepatic routes, CAZ and FEP are mainly excreted by the kidneys [47]. For MEM, older age (>70 years) has been found to be a predictor of lower CL and higher AUC, reflecting the relationship between aging and drug disposition [55]. Our results have also stressed the strong predictive value of body weight in the prediction of β-lactam Vd, CL and AUC.

The present models provide the PK information necessary for achieving the so-called dual dosage individualization. Such a practice actually takes into account both PK and PD parameters, named efficacy indices, when designing the dosage regimen [15,16]. Three efficacy indices have received increased emphasis by clinicians: the ratio of maximal concentration to minimal inhibitory concentration (MIC) of the infecting pathogen (Cmax/MIC), the percentage of the dosage interval with concentrations exceeding the MIC (T [%] ≥MIC) and the ratio of AUC during a 24-h interval to MIC (AUC24/MIC). To perform dual dosage individualization in clinical practice, it is necessary to select the appropriate efficacy index that correlates best with the therapeutic efficacy. While Cmax/MIC and AUC24/MIC are believed to better predict the therapeutic outcome for aminoglycosides, T [%] ≥MIC is considered to be the most relevant index indicating the β-lactam efficacy [11–14,56–58]. Furthermore, Schentag et al. [59] support the validity of AUC24/MIC as a universal efficacy index. When the efficacy index target and the MIC breakpoint of the infecting pathogen are known, rational drug dosage can be designed using Eqs. (3) [27], (4) and (5) [23]:

\[
\frac{C_{max}}{MIC} = \frac{\text{Dose}}{t_{inf} \cdot k_e \cdot V_d \cdot MIC} \left( \frac{1 - e^{-k_e \cdot t_{inf}}}{1 - e^{-k_e \cdot \tau}} \right)
\]

(3)

\[
T[\%] ≥ MIC = \ln \left( \frac{\text{Dose}}{V_d \cdot MIC} \right) \cdot \frac{t_{1/2}}{0.693} \cdot \frac{100}{\tau}
\]

(4)

\[
\frac{\text{AUC}_{24}}{MIC} = \frac{\text{Dose}}{V_d \cdot MIC} \cdot \frac{t_{1/2}}{0.693} \cdot \frac{24}{\tau}
\]

(5)

Table 3

Predictive performance of models predicting the β-lactam Vd, CL and AUC.

<table>
<thead>
<tr>
<th>Predicted PK parameters</th>
<th>n</th>
<th>MPE [%]</th>
<th>RMSE [%]</th>
<th>Patients [%] with PE [%] ≥X or ≤−X</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X=20% X=30% X=40%</td>
</tr>
<tr>
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PIP, piperacillin; CAZ, ceftazidime; FEP, cefepime; MEM, meropenem; Vd, volume of distribution; CL, total clearance; AUC, area under the serum concentration-time curve; n, number of patients; MPE, mean prediction error; RMSE, root mean square error; PE, prediction error.

Fig. 10. Observed versus predicted area under the serum concentration-time curve (AUC) of (A) piperacillin, (B) ceftazidime, (C) cefepime and (D) meropenem in critically ill septic patients.
where $t_{0.5}$ is the infusion duration (h), $k_e$ is the elimination rate constant (h$^{-1}$), $τ$ is the dosage interval (h), $dose$ is expressed in mg/kg, $\text{Vd}$ in L/kg, $t_1/2$ in h, and MIC in mg/L.

In our institution, the Sawchuk–Zaske method is daily applied in a TDM software–PharMonitor—optimally adjust the dosage regimens of four aminoglycosides (AMK, gentamicin, tobramycin and netilmicin) [37]. By integrating the present empirical models in the software, easy, rapid and cost-effective optimization of the β-lactam dosage regimens could be performed using the appropriate efficacy index. It should be emphasized that the dosage regimen obtained from such PK modeling equations remain to be validated by appropriate medical expertise taking into account the clinical status of the patient.

AMK, frequently prescribed in Europe, has been selected in our study. However, due to close chemophysical and PK properties among aminoglycosides, it is likely that similar conclusions could be reached from the use of other aminoglycosides such as gentamicin, whose the consumption is larger in USA and Japan.

In an attempt to promote optimal use of antibiotics in critically ill septic patients, the authors have developed empirical models to predict four β-lactams PK from amikacin routine clinical PK monitoring. In these models, the best predictor was one of the amikacin PK parameters obtained from PharMonitor. Other variables included fluid resuscitation, renal and hepatic biomarkers, age and body weight. The application of such models could contribute to a better therapeutic management of these patients.

Acknowledgments

The study was supported by AstraZeneca, Wyeth Pharmaceuticals, GlaxoSmithKline Pharmaceuticals and Bristol-Myers Squibb. The authors acknowledge the thoughtful assistance of the nursing staff of the intensive care units. The authors have no conflicts of interest that are directly relevant to the content of this study.

References


