Population pharmacokinetics of imipenem in critically ill patients with suspected ventilator-associated pneumonia and evaluation of dosage regimens.

Camille Couffignal, Olivier Pajot, Cédric Laouénan, Charles Burdet, Arnaud Foucrier, Michel Wolff, Laurence Armand-Lefevre, France Mentré, Laurent Massias

Title:

Population pharmacokinetics of imipenem in critically ill patients with suspected ventilator-associated pneumonia and evaluation of dosage regimens

Short title:

Population pharmacokinetics of imipenem in critically ill patients

Authors:

C Couffignal[1,6,7], O Pajot[2], C Laouénan[1,6,7], C Burdet[1,6,7], A Foucrier[3], M Wolff[3,6,7], L Armand-Lefevre[4,6,7], F Mentré[1,6,7] and L Massias[5,6,7]

(1) AP-HP, Hop Bichat, Biostatistics Dept, Paris, France

(2) Hop V Dupouy, Intensive Care Unit, Argenteuil, France

(3) AP-HP, Hop Bichat, Intensive Care Unit, Paris, France

(4) AP-HP, Hop Bichat, Bacteriology Dept, Paris, France

(5) AP-HP, Hop Bichat, Pharmacy Dept, Paris, France

(6) IAME, UMR 1137, Univ Paris Diderot, Sorbonne Paris Cité, F-75018 Paris, France

(7) IAME, UMR 1137, INSERM, F-75018 Paris, France

Correspondence:

Camille Couffignal

Pôle Santé Publique, Recherche Clinique et Information Médicale
Service de Biostatistiques
Hôpital Bichat
UMR 1137 INSERM - Université Paris Diderot - UFR de Médecine
16 rue Henri Huchard - 75018 Paris
tel : 01 57 27 75 35 - fax : 01 57 27 75 21
email: camille.couffignal@inserm.fr

Keywords:

Imipenem, Population pharmacokinetics, critical care, Ventilator-associated pneumonia

Word count: 3630 words

3 Tables (1 on supplementary materials)

6 Figures (3 on supplementary materials)

Abstract:

Objectives: Significant alterations in the pharmacokinetics (PK) of antimicrobials have been reported in critically ill patients. We describe PK parameters of imipenem in intensive care unit (ICU) patients with suspected ventilator-associated pneumonia (VAP) and evaluate several dosage regimens.

Methods: This French multicentre, prospective, open-label study was conducted in ICU patients with a presumptive diagnosis of Gram-negative bacilli VAP who empirically received imipenem I.V. q8h. Plasma imipenem concentrations were measured during the 4th imipenem infusion using 6 samples (trough, 0.5, 1, 2, 5 and 8 hours). Data were analysed with a population approach using the SAEM algorithm in Monolix 4.2. A Monte Carlo simulation was performed to evaluate six dosage regimens: 500, 750 or 1000mg with administration q6h or q8h. The pharmacodynamic target was defined as the probability of achieving a fractional time (fT) above minimum inhibitory concentration (MIC) greater than 40%.

Results: Fifty-one patients were included in the PK analysis. Imipenem concentration data were best described by a two-compartment model with three covariates (creatinine clearance, total body weight and serum albumin). Estimated clearance (between-subject variability) was 13.2 L/h (38%), and estimated central volume 20.4 L (31%). At an MIC of 4 µg/mL, the probability of achieving 40% fT >MIC was 91.8%, for 0.5-h infusions of 750mg q6h, 86.0% of 1000mg q8h and 96.9% of 1000mg q6h.

Conclusion:

This population PK model accurately estimated imipenem concentrations in ICU patients. The simulation showed that for these patients the best dosage regimen of imipenem is 750mg q6h and not 1000mg q8h.

What is already known about this subject?

In critically ill patients, there are significant alterations in antimicrobials pharmacokinetics (PK) and high MICs bacteria. Pharmacodynamic target for imipenem, widely used in this specific population, is based on time over MIC, but few data is available for imipenem PK in these patients and dosage regimen have not been evaluated.

What this study adds?

Using a PK population approach, our study showed in critically ill patients a slight increased clearance and twice increased distribution volume of imipenem, compared to healthy patients. We also demonstrated that for 2-to-4 µg/mL MICs bacteria, a 750 mg q6h dosage regimen allowed to reach a 40% fractional time over MIC.

Introduction

Imipenem was the first licensed antibiotic of the carbapenem class and has been widely used for more than 30 years, for hospital-related infections caused by resistant Gram-negative bacilli. Due to its broad spectrum, imipenem is often prescribed for initial empirical treatment of ventilator-associated pneumonia (VAP) in critically ill patients with risk factors for multidrug-resistant Gram-negative bacilli (1,2). It is a hydrophilic molecule characterised by a half-life ($t_{1/2}$) of one hour, low plasma protein binding (< 20%) and predominantly renal excretion unchanged close to 70% (3,4). In healthy subjects, the clearance is 12.1 L/h and the volume of distribution (Vd) of the central compartment is 9.6 L after 1000 mg every 8 hours (q8h) with 0.5-hour infusion (5). Imipenem has a time-dependent bactericidal activity and the pharmacodynamic (PD) parameter associated with its bactericidal effect is the fractional time (fT) when concentration is above the minimum inhibitory concentration (MIC). Imipenem has a post-antibiotic effect of 2 to 6 hours against most Gram-negative bacilli. Antimicrobial activity is optimised when the fraction of time above MIC (fT > MIC) is greater than 40% (6,7), but for critically ill patients some studies suggest an optimal fT > MIC of 100% (8,9).

In critically ill patients , the pharmacokinetic (PK) properties of drugs are modified with an increase in Vd, fluctuation of plasma clearance, presence of oedema, and drug-drug interaction (10–13), resulting in a lesser or higher drug exposure.

In addition to changes in PK characteristics of ICU patients, there is a worrisome increase in the incidence multiresistant Gram-negative bacilli, especially in the ICU. In this context, dosage regimens of antibiotics in the ICU must be adapted. Currently clinicians tend to increase the doses of antibiotics or change the dosage schedule without customizing antibiotic regimens according to the host and the offending pathogen.

Although imipenem is widely used in critically ill patients, data allowing optimisation of its administration are surprisingly scarce. Published PK studies with data in these patients are either of

imperfect design (14) or have a small number of subjects (15–19). Among these studies, three have specifically analysed imipenem PK variability in ICU patients with VAP.

Some authors have evaluated several dosage regimens of antimicrobials in critically ill patients. For aminoglycoside antibiotics, Conil et al. (20) showed the impact of adapting the regimen on PD targets ($80 < AUC < 125$ mg.L^{-1}.h and peak > 10 mg.L^{-1}) after simulation dosage regimens in ICU patients with nosocomial infections. For meropenem, an antibiotic of the same class as imipenem, Crandon *et al* (21) evaluated the concentration-time profile in ICU patients with VAP in order to limit the potential inadequacies noted for current dosage regimens.

The aim of our study was to estimate the PK parameters of imipenem and their variability in ICU patients with suspected VAP, using a population approach to determine the influence of clinical and biological covariates for imipenem. We performed a Monte Carlo simulation to evaluate several dosage regimens based on the PD parameter ($fT > MIC$) for the range of clinical relevant MICs in ICU.

Materials and Methods

Study design and population

IMPACT, a multicentre, prospective, open-label trial was conducted in three ICUs of two French hospitals (Hôpital V Dupouy, polyvalent ICU, Argenteuil, France; AP-HP, Hôpital Bichat, medical ICU and surgical ICU, Paris, France). All patients, receiving empirically imipenem I.V. for presumptive diagnosis of Gram-negative bacilli VAP, were screened from 2008 to 2010. Inclusion criteria were: (i) male or female over 18 years of age, (ii) use of mechanical ventilation for more than 48 hours, (iii) clinical suspicion of VAP (1) (new or persistent radiological infiltrate and one of following criteria: purulent tracheal aspiration or temperature ≥ 38°3 or leucocytosis > 10000/mL) (iv) VAP with high risk of multiresistant bacteria (1) (at least 6 days of mechanical ventilation or antibiotic treatment within 15 days). Non-inclusion criteria were (i) time between diagnosis and first antibiotic therapy ≥ 24 h (ii) expected death within 48 h (iii) creatinine clearance < 10 mL/min or renal replacement therapy.

At inclusion, all patients were treated with a single infusion of amikacin (20 mg/kg) and imipenem q8h (500 to 1000 mg) administered as 0.5-hour infusions. The imipenem dose was defined by the protocol previously established according to the creatinine clearance estimated by Cockcroft-Gault (ClCG) of each patient at inclusion, as recommended by the European Medicine Agency (ClCG>70 ml/min/1.73 m2: 1000 mg q8h; ClCG>30 ml/min/1.73 m2 and ≤70 ml/min/1.73 m^2: 750 mg q8h; ClCG ≤30 ml/min/1.73 m^2: 500 mg q8h).

The study was conducted in accordance with good clinical practice and was approved by the ethics committee (Comité de Protection des Personnes Ile de France I). All patients or their legal representative signed an informed consent form.

Clinical Trial Registration: http://www.clinicaltrials.gov; unique identifier: NCT00950222.

Sampling Procedure and Analytical Methods

Imipenem concentrations were measured at steady state after the 4th dose i.e. between 24 and 32 hours after the first infusion of imipenem. Six blood samples per patient were collected immediately before and at 0.5, 1, 2, 5 and 8 hours after the 4th infusion for concentration measurement.

Blood samples were retrieved from 4 mL of heparin and immediately centrifuged at 4000 rpm. Plasma was then stabilised within ½ hour after collection, by 4-morpholine propane sulphonic acid (MOPS) in ethylene glycol and immediately frozen at -80 °C. Plasma imipenem concentrations were determined after processing the samples by ultrafiltration, using high-performance liquid chromatography (HPLC) on an Interchrome© YP5C18 25QS reverse phase column (length 25 cm, internal diameter 4.6 cm). UV detection was performed at 302 nm (22). Chromatographic peaks were integrated and imipenem concentrations calculated using Empower 2 software Water®. The lower limit of quantification (LOQ) was 0.5 mg/L.

Blood sample analysis was centralised in the pharmacology-toxicology laboratory of the Hôpital Bichat, AP-HP, Paris, France.

Population pharmacokinetic model building

Population PK analysis was performed using MONOLIX 4.1.2 software (www.lixoft.eu). Population PK parameters were estimated by maximum likelihood using the stochastic approximation expectation maximisation (SAEM) algorithm (23). The SAEM algorithm is an expectation maximisation (EM) algorithm extension in the nonlinear mixed-effects models where the parameter estimation was computed by the maximum likelihood estimator of the parameters without any approximation of the model as linearization. Briefly, SAEM converges to maximum likelihood estimates by repeatedly alternating between the E and M steps. Then, the expectation of the complete likelihood is computed according to a stochastic approximation (25).

The full maximum likelihood estimation allows to take into account the data below quantification limit (BQL) (24). BQL data are considered as left-censored observations, indeed in that case the data

y_{ij} is not observed but we only know that it is below the LOQ. The extension of the SAEM algorithm in MONOLIX to consider BQL realized a simulation of the left-censored data in a right-truncated Gaussian distribution with an integration below limit of quantification to obtain probability of BQL. It is very similar to the method call 'M3' in NONMEM for handling BQL data (26).

Structural and statistical model

In the first step, a basic population PK model without covariates was developed. For the structural PK model, one- and two-compartment models were compared. Exponential random effects were assumed to describe between-subject variability: e.g. for clearance (CL) of subject i, $CL_i = CL_{pop} \times e^{\eta_{CL,i}}$ where CL_{pop} is the population parameter estimate, $\eta_{CL,i}$ is the individual random effect. The random effects were first supposed to be independent with diagonal variance-covariance matrix Ω and then possible correlations between random effects were tested in this variance-covariance matrix. Additive, proportional and combined error models were tested. The most appropriate pharmacostatistical model was selected on the basis of the following criteria: (i) smaller value of Bayesian information criterion (BIC); (ii) adequate goodness-of-fit (GOF) plots; (iii) low relative standard error (RSE) in estimated PK parameters.

Covariate analysis

From the basic model, twelve covariates were studied and chosen for their impact on the PK parameters specifically in the ICU in accordance with published data. These 12 covariates were: age, gender, total body weight at inclusion and total body weight change (between the 4th dose and admission); three specific ICU scores, namely SAPS II (27), the SOFA score (28) and the oedema score (ES) (29); serum albumin and four-hour creatinine clearance ($CrCl_{4h}$) (30); positive end-expiratory pressure (PEEP), PaO2/FiO2 ratio, and the presence of septic shock. These covariates were recorded at the 4th dose of imipenem except for SAPS II and weight, which were measured both at admission and inclusion. Urine samples for $CrCl_{4h}$ were collected when the 4th infusion of imipenem had started.

CrCl measurement over 4 hours was assumed to be a true reflection of renal function during the 4th infusion (31,32). Missing values for tested covariates were imputed to the median value observed in the analysis population.

The parameter-covariate relationships were modelled multiplicatively as follows (e.g. for imipenem clearance CL): for continuous covariates, $CL_i = CL_{pop} \times (\frac{COV_i}{COV_{median}})^{\beta} \times e^{\eta_{CL,i}}$ where β is the covariate effect to be estimated, COV_i is the value for the subject i; COV_{median} is the median value of covariates; for binary covariates, $CL_i = CL_{pop} \times e^{\beta.COV_i} \times e^{\eta_{CL,i}}$ where COV_i takes a value of 0 or 1. For all covariates, binary or continuous, the unit of β is the log of the unit of the associated parameter.

Covariates were selected with a forward method using BIC (33). First, a model with one covariate was selected with the smallest BIC. Then, the model with two covariates was selected similarly. The addition of covariates was stopped when no further decrease of BIC was obtained. The covariates model was finalised with a backward selection, removing covariates one by one, using the Likelihood Ratio Test (LRT). A covariate was retained in the model if the LRT was significant ($p < 0.05$) when it was removed from the full model. In the final model, the 95% confidence interval of each parameters was determined from 1000 nonparametric bootstraps based resampling (34).

Model evaluation

Evaluation of the model was based on GOF plots. The model was first evaluated using observations versus individual and population predictions plots and usual residual-based plots (individual weighted residuals [IWRES] plot and population weighted residuals [PWRES] plot). It was then assessed using simulation-based plots, (visual predictive check (VPC) plot and normalised prediction distribution error (NPDE) versus time. The VPC plot showed the 10th, 50th, and 90th percentiles of observed data over time and their corresponding 90% prediction intervals calculated from 500 Monte Carlo samples (simulated using the model, the parameter estimates and the design of the dataset). NPDE was built from the percentile derived from VPC prediction. The plot of NPDE takes

into account the full predictive distribution of each individual observation and the various imipenem doses. As only few patients had different doses of imipenem and as we plot NPDE, we did not perform a prediction corrected VPC (35).

Model evaluation was performed for both the basic model and the final model with covariates.

Monte Carlo simulation for dosage regimen evaluation

A Monte Carlo simulation was performed using the final PK model with covariates to predict the distribution of plasma imipenem concentrations and to estimate the PD parameter fT > MIC for several current dosage regimens and various MIC values. Six usual dosage regimens were studied: 500, 750 and 1000 mg with administration q6h or q8h. We simulated 1000 patients with a set of covariates re-sampled among the observed covariates of included patients and a vector of random effects drawn from the estimated distribution. The concentration-time profile of the 1000 virtual patients was simulated at steady state for the six dosage regimens.

The MIC targets were selected from the European Committee on Antimicrobial Susceptibility Testing (EUCAST(36)) data and ranged from 0.06 to 32 µg/mL. Two specific MIC, 2 µg/mL and 4 µg/mL, were studied. These MICs were the limited sensitivity breakpoint of imipenem currently observed for Gram-negative bacilli isolated in the ICU (Enterobacteriaceae species and P*seudomonas aeruginosa,* respectively).

The time for which the imipenem concentration remained above the MIC at steady state was calculated as a cumulative percentage over a 24-hour period and the probability of pharmacodynamic target attainment (PTA) was assessed as a fraction that achieved 40% fT > MIC or 100% fT > MIC.

Results

Patients

Sixty-three patients were included in the IMPACT study. Twelve patients were excluded from the PK analysis: three lacking a kinetic profile and nine who did not receive four doses of imipenem. Fifty-one patients were included in the PK analysis, 41 of whom were males (80%), ranging in age from 28 to 84 years (median 60 years). At inclusion, median total body weight was 77 kg (range [45-126]). All patient characteristics are summarised in Table 1. Reasons for admission to the ICU were medical in 40 patients (78%) and surgical for 11 patients (22%), and the SAPS II at admission was 43 [17-80]. The median duration of stay in the ICU and of mechanical ventilation before inclusion was 8 days [1-60] and 8 days [5-60], respectively. Antibiotic therapy was prescribed to 48 patients (94%) in the three months before admission, including 11 patients (30%) who previously received imipenem.

Four patients (9%) received 500 mg of imipenem, 15 (29%) 750 mg and 32 (62%) 1000 mg with the same dose interval q8h.

Population pharmacokinetic analysis

A total of 297 samples were available for PK modelling with a median of 6 samples [3-6] per individual (Figure 1). Imipenem concentrations at peak (0.5 h) and trough were 34.1 mg/L [12.3-67.5] and 1.9 mg/L [0.5-10.1], respectively. Nine percent of imipenem concentrations were below the limit of quantification (BQL). One patient received the 4^{th} dose 5 hours late.

Imipenem PK concentrations were best described by a two-compartment model. An exponential random effects model described the between-subject variability in clearance CL and volume of distribution of the central compartment V_1. Since the variability of intercompartmental clearance Q and the volume of distribution of the peripheral compartment V_2 were very low, the between-subject variability was not estimated and was taken as zero. A proportional model was used to describe the residual variability.

As shown in Table 2, estimated imipenem CL was 13 L/h, Q 10.1 L/h and the volumes V_1 and V_2 were 22.4 L and 9.9 L, respectively. A correlation between CL and V_1 was retained in the basic model and estimated as 0.48. The GOF plots of the basic model were satisfactory (plots not shown).

Model with covariates

The best model with one covariate included the effect of 4-hour creatinine clearance ($CrCl_{4h}$) on CL. Covariate selection was continued up to a model with four covariates; the model with five covariates had a larger BIC (Table 3).

The backward selection was then performed from the model with the four following covariates: $CrCl_{4h}$, age, serum albumin and total body weight. Only three covariates were significant using the LRT and kept in the final model: $CrCl_{4h}$ on CL, serum albumin (imputed to median value for 8 patients with missing data) and total body weight on V_1. Imipenem CL was found to increase with $CrCl_{4h}$. V_1 was found to increase with total body weight and decrease with serum albumin (Figure 2).

The introduction of $CrCl_{4h}$ alone reduced the variability of CL (ω_{CL}) from 48% to 38%. The introduction of weight and serum albumin reduced the variability of V_1 from 48% to 31%. The final PK parameters are summarised in Table 2. All were reliably estimated, as reflected by the small RSEs from observed Fisher Information Matrix. The results of bootstrap medians and 95% CI were consistent except for the between-subject variability ω_{V1} and the correlation. Nevertheless the bootstrap analysis confirmed the reliability and robustness of the parameter estimates and thus the final model with covariates was representive. Estimated parameters were similar in the analysis of the 43 patients with no missing albumin data (results not shown).

Model evaluation

The GOF plots of the final PK model with covariates are shown in Figure 3 and Figure 4. The model adequately described the observations as shown by the plots of observations versus population and individual predictions with the exception of the highest concentrations. Moreover, the NPDE plot

versus predictions and the IWRES show no trend. The VPC plot and the NPDE plot presented in Figure 4 as a function of time from first dose indicate a good predictive performance of the model.

Monte Carlo simulation for dosage regimen evaluation

Using the simulated concentration-time profiles at steady-state, the PTA (40% or 100% fT > MIC) was calculated for the current dosage regimens 500, 750 and 1000 mg q6h or q8h. As shown in Figure 5 (a), all simulated patients had a fT > MIC greater than 40% for MIC from 0.06 to 1 μg/mL for the 6 dosage regimens. For MIC = 2 μg/mL, 86% of patients had the PTA at 40% with 500 mg q8h, 96.9% with 500 mg q6h; 95.3% with 750 mg q8h, 99.1% with 750 mg q6h; 97.9% with 1000 mg q8h and 99.4% with 1000 mg q6h. Figure 5 (b) shows the probability of fT > MIC greater than 100% with the 6 different dosage regimens. The percentage of patients was higher with the q6h regimen than with the q8h regimen, whatever the dose. For MIC = 4 μg/mL, 5% of simulated patients had the PTA at 100% with 500 mg q8h and 18.7% with 500 mg q6h; 14.3% with 750 mg q8h and 32.5% with 750 mg q6h; 20.9% with 1000 mg q8h and 45% with 1000 mg q6h.

These results were confirmed by the simulated median concentration-time profile after four doses of imipenem (study protocol) as shown in Figure 6. The median patient with the 1000 mg q8h regimen did not achieve the PD target of MIC = 2 μg/mL. The median patient with 750 mg or 1000 mg q6h achieved the PD target of MIC = 2 μg/mL, but not for MIC = 4 μg/mL.

We also explored the impact of each of the three significant covariates, namely $CrCl_{4h}$, total body weight and serum albumin, on PTA. In Table S1 (of supplementary materials), we computed the PTA for the dose of 1000 mg q8h (the dosage regimen of the protocol) and 750 mg q6h (same daily dose) for three percentiles of each covariate (10^{th}, 50^{th} and 90^{th}), assuming the two remaining covariates were at their median value. For both dosing regimens, 40% fT > MIC was obtained for the target MICs 2 μg/mL and 4 μg/mL for all values of the covariates. Figure S1 shows the concentration profile at steady state for 750 mg q6h for the various covariate values. It illustrates the rather limited impact of covariates on fT > MIC for that dosage regimen.

Discussion

We studied the pharmacokinetics of imipenem after I.V. infusion in 51 critically ill patients hospitalised in an ICU with suspected Gram negative VAP, using a population approach. We found that imipenem concentrations were best described by a two-compartment model in accordance with previously published studies (14,17,18). The strength of our study is the number of patients with prospective collection of kinetic profiles with 6 points and a central laboratory for concentration assessment. To the best of our knowledge, the present study is the first study of imipenem PK using a population approach in the ICU.

In the population PK study performed by Lee et al. (5) in healthy subjects, estimated imipenem clearance was 12.1 L/h and estimated central volume was 9.7 L. In ICU patients, we found a very similar clearance. The volume of distribution was estimated to 20.4 L in the final model, which is twice higher than that described in a healthy population. This increase is consistent with the clinical status of ICU patients. Indeed, inflammatory response in sepsis lead to an increased capillary permeability, with fluid flow to the extracellular compartment (edema development). McKindley et al. (15) reported an increased volume of distribution in ICU patients with VAP. Similarly, Novelli et al. (17) enhanced the impact of sepsis on the volume of distribution with a new compartment, the third compartment for critically ill patients with sepsis.

For covariate selection we used a standard stepwise approach rather than a more modern approaches (such as the lasso method associated with cross-validation (37)). Results of the selection steps were very consistent with our rich pharmacokinetic design. Of the 12 covariates studied, we found that $CrCl_{4h}$, total body weight and serum albumin have a significant impact on the PK variability of imipenem. The addition of these three covariates reduces the variability of imipenem clearance and central Vd with a decrease of 10% for CL and 17% for V_1. A recent study by Yoshizawa et al. (38) also showed the impact of creatinine clearance on imipenem clearance in patients with altered renal function. The other covariates tested, namely age and body weight, were not kept in their model. Estimates of pharmacokinetic parameters CL and V_1 were 8 L/h and 11.4 L, respectively, with a

median CrCL = 54.1 mL/min, and were lower than those estimated in our population. In our study, we observed high values of creatinine clearance. These high values are consistent with the hyperdynamic state of sepsis patients and confirmed the physiological impact on the PK parameters (39). It is therefore necessary to regularly control this creatinine clearance parameter in ICU to limit an effect on the clearance of imipenem although this effect was limited in our final PK model (Figure S1). A similar process of recorded creatinine clearance was previously described by Belzberg et al. (14) during 2 hours with maximum value of 408 mL/min. in accordance with our study, this study did not found an influence of creatinine clearance on imipenem clearance but an increase of distribution volume.

The hydrophilic nature of imipenem makes it sensitive to changes in the distribution of body fluids. Its volume of distribution is affected by all disorders resulting in an increase of the extracellular compartment such as sepsis or clinically revealed by edema. In our study, we did not find any effect of edema on imipenem volume of distribution in the PK model but total body weight and serum albumin were found to influence significantly the distribution of imipenem and probably were reflected the physiological characteristics encountered in the ICU. The same increase of central volume was also observed for another antibiotic class, the aminoglycosides. Tanigawara et al. (40) showed a significant increase of volume of distribution in a comparative study between healthy subjects and patients with pneumonia or sepsis treated by arbekacin hydrophilic and low protein binding antibacterial agents as imipenem. For results of Figure 2 and total body weight estimate coefficient, we evaluated the volume with a coefficient of total body weight fixed to one. The volumes expressed as L/kg were very similar between the final model and the total body weight coefficient model, 0.26 L/kg and 0.27 L/kg respectively. Due to the hydrophilic property of this antibacterial agent, we wished to evaluate other weight metrics (as ideal body weight or lean body weight) but these parameters could unfortunately not be collected during patient monitoring. No other covariates, especially ICU scores, were found in the PK model and considered for determination of the dosage regimen of imipenem.

With the PK results, we also performed a Monte Carlo simulation to evaluate several dosage regimens with doses given q6h or q8h. In the context of suspected VAP due to Gram-negative bacilli, we focused our simulations on the target MICs of 2 and 4 µg/mL (sensitivity breakpoint of Enterobacteriaceae species and *Pseudomonas aeruginosa*, respectively). With the same daily dose of 3 g, a q6h infusion led to a PD objective greater than 40% fT > MIC for those two target MICs. Despite their impact on the variability of PK parameters, the covariates lead to rather small changes in PK parameters and concentration profiles and thus have a limited effect on PTA, and we show rather small changes in the PTA 40% fT > MIC. Our evaluation of the 3 g daily dose has confirmed that q6h is a good dosage regimen for use in the ICU. This dose did not exceed the threshold of toxicity and the q6h regimen was optimised to take into account the higher PK variability seen in critically ill patients.

Conclusion

Our results demonstrate that imipenem pharmacokinetics vary in ICU patients. Imipenem clearance CL and central volume V_1 were best estimated with three covariates whose influence on pharmacokinetic estimates was limited. Using population pharmacokinetic parameters, we showed that an infusion 750 mg q6h dosage regimen (3 g daily dose) is needed to achieve adequate pharmacodynamics, i.e., a fraction of time above MIC greater than 40% for usual the MICs of 2 and 4 µg/mL.

Funding Statement

This study was funded by the Contrat d'Initiation à la Recherche Clinique 2006 (Assistance Publique-Hôpitaux de Paris, Département de la Recherche Clinique et du Développement, CRC 06049)

All authors have completed the Unified Competing Interest format http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

References

1. American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2005 Feb 15;171(4):388–416.
2. Joseph J, Rodvold KA. The role of carbapenems in the treatment of severe nosocomial respiratory tract infections. Expert Opin Pharmacother. 2008;9(4):561–75.
3. Balfour JA, Bryson HM, Brogden RN. Imipenem/cilastatin: an update of its antibacterial activity, pharmacokinetics and therapeutic efficacy in the treatment of serious infections. Drugs. 1996;51(1):99–136.
4. Wolff M, Joly-Guillou M, Pajot O. Les carbapénèmes. Réanimation. 2009;18, Supplement 2:S199–S208.
5. Lee LS, Kinzig-Schippers M, Nafziger AN, Ma L, Sörgel F, Jones RN, et al. Comparison of 30-min and 3-h infusion regimens for imipenem/cilastatin and for meropenem evaluated by Monte Carlo simulation. Diagn Microbiol Infect Dis. 2010 Nov;68(3):251–8.
6. Rodloff AC, Goldstein EJC, Torres A. Two decades of imipenem therapy. J Antimicrob Chemother. 2006;58(5):916–29.
7. Mouton JW, Touzw DJ, Horrevorts AM, Vinks AA. Comparative pharmacokinetics of the carbapenems: clinical implications. Clin Pharmacokinet. 2000;39(3):185–201.
8. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis. 1998;26(1):1–10.
9. Zelenitsky SA, Ariano RE, Zhanel GG. Pharmacodynamics of empirical antibiotic monotherapies for an intensive care unit (ICU) population based on Canadian surveillance data. J Antimicrob Chemother. 2011 Feb;66(2):343–9.
10. Roberts JA, Lipman J. Pharmacokinetic issues for antibiotics in the critically ill patient. Crit Care Med. 2009;37(3):840–51.
11. Pea F, Viale P, Furlanut M. Antimicrobial therapy in critically ill patients: a review of pathophysiological conditions responsible for altered disposition and pharmacokinetic variability. Clin Pharmacokinet. 2005;44(10):1009–34.
12. Mehrotra R, De Gaudio R, Palazzo M. Antibiotic pharmacokinetic and pharmacodynamic considerations in critical illness. Intensive Care Med. 2004;30(12):2145–56.
13. Boucher BA, Wood GC, Swanson JM. Pharmacokinetic changes in critical illness. Crit Care Clin. 2006;22(2):255–71.
14. Belzberg H, Zhu J, Cornwell EE 3rd, Murray JA, Sava J, Salim A, et al. Imipenem levels are not predictable in the critically ill patient. J Trauma. 2004;56(1):111–7.
15. McKindley DS, Boucher BA, Hess MM, Croce MA, Fabian TC. Pharmacokinetics of aztreonam and imipenem in critically ill patients with pneumonia. Pharmacotherapy. 1996;16(5):924–31.
16. Tegeder I, Schmidtko A, Bräutigam L, Kirschbaum A, Geisslinger G, Lötsch J. Tissue distribution of imipenem in critically ill patients. Clin Pharmacol Ther. 2002;71(5):325–33.
17. Novelli A, Adembri C, Livi P, Fallani S, Mazzei T, De Gaudio AR. Pharmacokinetic evaluation of meropenem and imipenem in critically ill patients with sepsis. Clin Pharmacokinet. 2005;44(5):539–49.
18. Sakka SG, Glauner AK, Bulitta JB, Kinzig-Schippers M, Pfister W, Drusano GL, et al. Population pharmacokinetics and pharmacodynamics of continuous versus short-term infusion of imipenem-cilastatin in critically ill patients in a randomized, controlled trial. Antimicrob Agents Chemother. 2007;51(9):3304–10.
19. Jaruratanasirikul S, Sudsai T. Comparison of the Pharmacodynamics of Imipenem in Patients with Ventilator-Associated Pneumonia Following Administration by 2 or 0.5 H Infusion. J Antimicrob Chemother. 2009;63(3):560–3.

20. Conil J-M, Georges B, Ruiz S, Rival T, Seguin T, Cougot P, et al. Tobramycin disposition in ICU patients receiving a once daily regimen: population approach and dosage simulations. Br J Clin Pharmacol. 2011;71(1):61–71.
21. Crandon JL, Ariano RE, Zelenitsky SA, Nicasio AM, Kuti JL, Nicolau DP. Optimization of meropenem dosage in the critically ill population based on renal function. Intensive Care Med. 2011;37(4):632–8.
22. Garcia-Capdevila L, López-Calull C, Arroyo C, Moral MA, Mangues MA, Bonal J. Determination of imipenem in plasma by high-performance liquid chromatography for pharmacokinetic studies in patients. J Chromatogr B Biomed Sci App. 1997 Apr 25;692(1):127–32.
23. Lavielle M, Mentré F. Estimation of Population Pharmacokinetic Parameters of Saquinavir in HIV Patients with the MONOLIX Software. J Pharmacokinet Pharmacodyn. 2007;34(2):229–49.
24. Samson A, Lavielle M, Mentré F. Extension of the SAEM algorithm to left-censored data in nonlinear mixed-effects model: Application to HIV dynamics model. Comput Stat Data Anal. 2006 Dec;51(3):1562–74.
25. Kuhn E, Lavielle M. Maximum likelihood estimation in nonlinear mixed effects models. Comput Stat Data Anal. 2005;49:1020–38.
26. Beal SL. Ways to fit a PK model with some data below the quantification limit. J Pharmacokinet Pharmacodyn. 2001 Oct;28(5):481–504.
27. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. J Am Med Assoc. 1993;270(24):2957–63.
28. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996;22(7):707–10.
29. Gómez CM, Cordingly JJ, Palazzo MG. Altered pharmacokinetics of ceftazidime in critically ill patients. Antimicrob Agents Chemother. 1999;43(7):1798–802.
30. Pickering JW, Frampton CM, Walker RJ, Shaw GM, Endre ZH. Four hour creatinine clearance is better than plasma creatinine for monitoring renal function in critically ill patients. Crit Care Lond Engl. 2012;16(3):R107.
31. Herrera-Gutiérrez ME, Seller-Pérez G, Banderas-Bravo E, Muñoz-Bono J, Lebrón-Gallardo M, Fernandez-Ortega JF. Replacement of 24-h creatinine clearance by 2-h creatinine clearance in intensive care unit patients: a single-center study. Intensive Care Med. 2007 Nov;33(11):1900–6.
32. Herget-Rosenthal S, Quellmann T, Linden C, Hollenbeck M, Jankowski V, Kribben A. How does late nephrological co-management impact chronic kidney disease? - An observational study. Int J Clin Pract. 2010 Dec;64(13):1784–92.
33. Mould DR, Upton RN. Basic concepts in population modeling, simulation, and model-based drug development-part 2: introduction to pharmacokinetic modeling methods. CPT Pharmacomet Syst Pharmacol. 2013;2:e38.
34. Thai H-T, Mentré F, Holford NHG, Veyrat-Follet C, Comets E. Evaluation of bootstrap methods for estimating uncertainty of parameters in nonlinear mixed-effects models: a simulation study in population pharmacokinetics. J Pharmacokinet Pharmacodyn. 2014 Feb;41(1):15–33.
35. Bergstrand M, Hooker AC, Wallin JE, Karlsson MO. Prediction-corrected visual predictive checks for diagnosing nonlinear mixed-effects models. AAPS J. 2011 Jun;13(2):143–51.
36. EUCAST. Breakpoint table for interpretation of MICs and zone diameters. [Internet]. [cited 2013 Nov 25]. Available from: http://www.eucast.org/
37. Ribbing J, Nyberg J, Caster O, Jonsson EN. The lasso--a novel method for predictive covariate model building in nonlinear mixed effects models. J Pharmacokinet Pharmacodyn. 2007 Aug;34(4):485–517.
38. Yoshizawa K, Ikawa K, Ikeda K, Kumon H, Ohge H, Morikawa N. Optimisation of imipenem regimens in patients with impaired renal function by pharmacokinetic-pharmacodynamic target

attainment analysis of plasma and urinary concentration data. Int J Antimicrob Agents. 2012;40(5):427–33.
39. De Paepe P, Belpaire FM, Buylaert WA. Pharmacokinetic and pharmacodynamic considerations when treating patients with sepsis and septic shock. Clin Pharmacokinet. 2002;41(14):1135–51.
40. Tanigawara Y, Sato R, Morita K, Kaku M, Aikawa N, Shimizu K. Population pharmacokinetics of Arbekacin in patients infected with methicillin-resistant Staphylococcus aureus. Antimicrob Agents Chemother. 2006 Nov;50(11):3754–62.

Figure legends:

Figure 1: Spaghetti plot of imipenem concentrations versus time following four doses for the 51 ICU patients included in the analysis. Data above LOQ are presented as blues circles, BQL data as red circles at LOQ.

Figure 2: Relationship between estimated individual pharmacokinetic parameters and covariates: (a) clearance vs. 4-hour creatinine clearance (b) central volume vs. total body weight (c) central volume vs. serum albumin. Model predictions are displayed as the red curve.

Figure 3: Goodness-of-fit plots for the final model with covariates: (a) Observations and (b) population weighted residuals (PWRES) versus population predicted values; (c) observations and (d) individual weighted residuals (IWRES) versus individual predicted values. Observations are plotted as blue circles and BQL data as red circles. LOWESS smoothed curve are plotted as blue curves.

Figure 4: (a) Visual Predictive Check (VPC) and (b) Normalized Prediction Distribution Error (NPDE) versus time since first dose for the final model. VPC details: the solid green lines indicate the $10^{th,}$ 50^{th} and 90^{th} percentiles for observed data. The shaded blue and pink areas represent 90% prediction intervals from the corresponding percentiles calculated from simulated data. Observations are plotted as blue circles and BQL data as red circles.

Figure 5: Simulated probabilities of pharmacodynamic target attainment versus MIC for various imipenem current dosage regimens at steady state (a) 40 % fT > MIC and (b) 100 % fT > MIC. Vertical lines are displayed for MIC = 2 µg/mL and MIC = 4 µg/mL which are the thresholds currently observed for Gram-negative bacteria in the ICU.

Figure 6: Predicted concentrations of imipenem for median value of parameters for 1000 mg q8h or 1000 mg q6h or 750 mg q6h.

Table 1: Characteristics at inclusion or at time of PK collection (4th dose) of the 51 ICU patients included in the PK analysis

Parameters	Value*
At inclusion	
Male	41 (80 %)
Age (years)	60 [28-84]
Total body weight (kg)	77 [45-126]
SAPS II	40 [19-74]
At time of 4th dose	
Weight change# (kg)	1.1 [-18.1-19.1]
SOFA	6 [2-14]
Oedema score	7 [0-18]
Serum albumin (g/L)**	18 [10-28]
$CrCl_{4h}$ (mL/min)	86.4 [9.1-571.4]
Shock	18 (35 %)
PEEP (cmH_2O)	6 [0-13]
PaO2/FiO2	182 [81-346]

* Values are expressed as median [min-max] or number (percent)

between the 4th dose and admission

** median value for 9 patients

Table 2: Population PK parameters of imipenem in 51 ICU patients

	Basic model		Final model				
	Value	RSE* (%)	Value	RSE* (%)	p-value**	Median bootstrap#	95% CIs bootstrap#
Fixed effects							
CL (L/h)	13.0	6	13.2	5		13.2	11.4 – 15.3
β_{CrCL4h} (log L/h)	-	-	0.2	19	$6.4\ 10^{-5}$	0.25	0.1 – 0.4
V_1 (L)	22.4	9	20.4	7		19.8	14.9 – 25.4
β_{Weight} (log L)	-	-	1.3	17	$1.3\ 10^{-4}$	1.2	0.6 – 2.2
$\beta_{Serum\ albumin}$ (log L)	-	-	-1.1	18	$1.8\ 10^{-4}$	-1.0	-1.8 – -0.5
Q (L/h)	10.1	28	12.2	25		12.3	4.7 – 20.3
V_2 (L)	9.9	14	9.8	13		10.5	6.9 – 13.7
Between-subject variability							
ω_{CL} (%)	48	10	38	13		36	26 – 49
ω_{V1} (%)	48	15	31	18		22	1 – 45
Correlation							
$\eta_{CL_i}\eta_{V_{1i}}$	0.48	29	0.51	28		0.79	-1 – 1
Residual variability							
σ (%)	33	4	33	3		34	26 – 41
BIC	1595	-	1560	-		-	

* RSE: relative standard error; ** Likelihood ratio test (LRT); # from 1000 bootstrap resampling.

Final population PK covariate model is: $CL_i = 13.2 \times (\frac{CrCL_i}{86.4})^{0.2}\ and\ V_{1i} = 20.4 \times (\frac{weight}{77})^{1.3} \times (\frac{albumin}{18})^{-1.1}$.

Table 2: Summary of covariates model building

Model	Number of covariates	- 2LL	BIC	ΔBIC
Basic model	0	1563	1595	-
CrCL on CL	1	1541	1577	-18
CrCL and age on CL	2	1536	1573	- 22
CrCL and age on CL Weight on V_1	3	1527	1571	- 24
CrCL and age on CL Weight and Alb on V1	4	1510	1557	- 38
CrCL and age on CL Weight, Alb and ES on V1	5	1508	1559	- 36

Alb = Serum albumin; -2LL = - 2 *log - likelihood; ΔBIC = BIC (model step) – BIC (basic

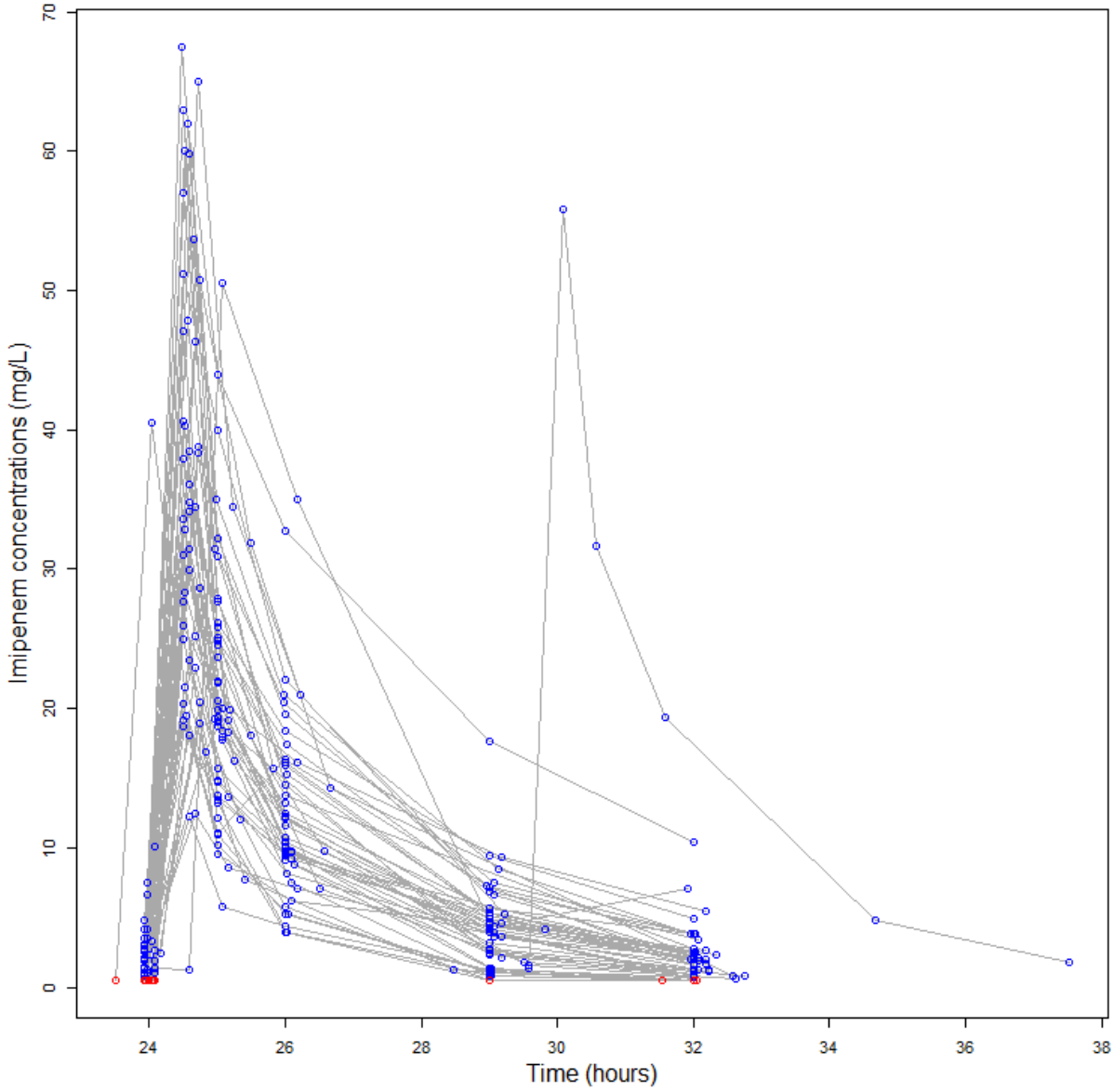

Imipenem concentrations (mg/L)
0
10
20
30
40
50
60
70
24
26
28
30
32
34
36
38
Time (hours)

Figure 1

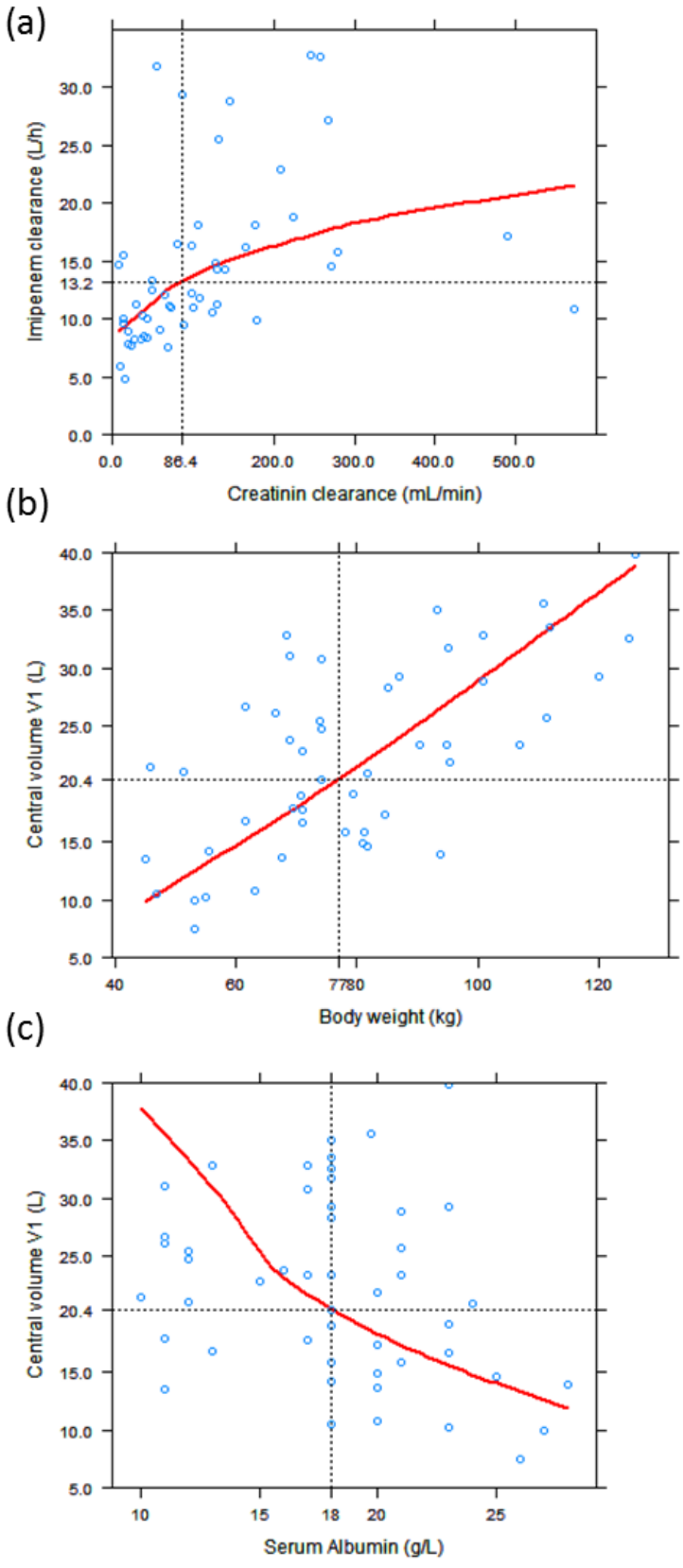

(a)
Imipenem clearance (L/h)
30.0
25.0
20.0
15.0
13.2
10.0
5.0
0.0
0.0
86.4
200.0
300.0
400.0
500.0
Creatinin clearance (mL/min)
(b)
Central volume V1 (L)
40.0
35.0
30.0
25.0
20.4
15.0
10.0
5.0
40
60
77 80
100
120
Body weight (kg)
(c)
Central volume V1 (L)
40.0
35.0
30.0
25.0
20.4
15.0
10.0
5.0
10
15
18
20
25
Serum Albumin (g/L)

Figure 2

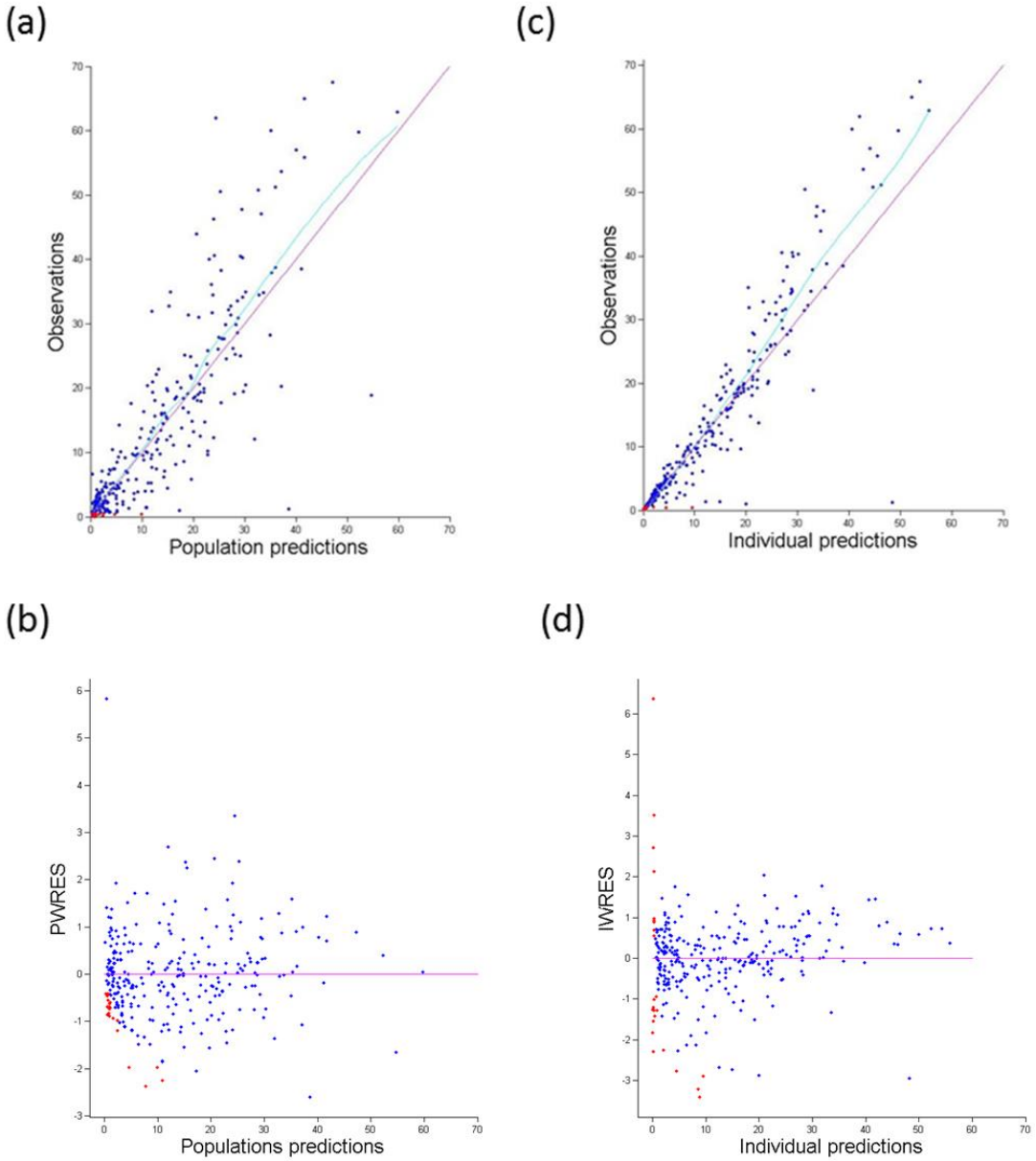
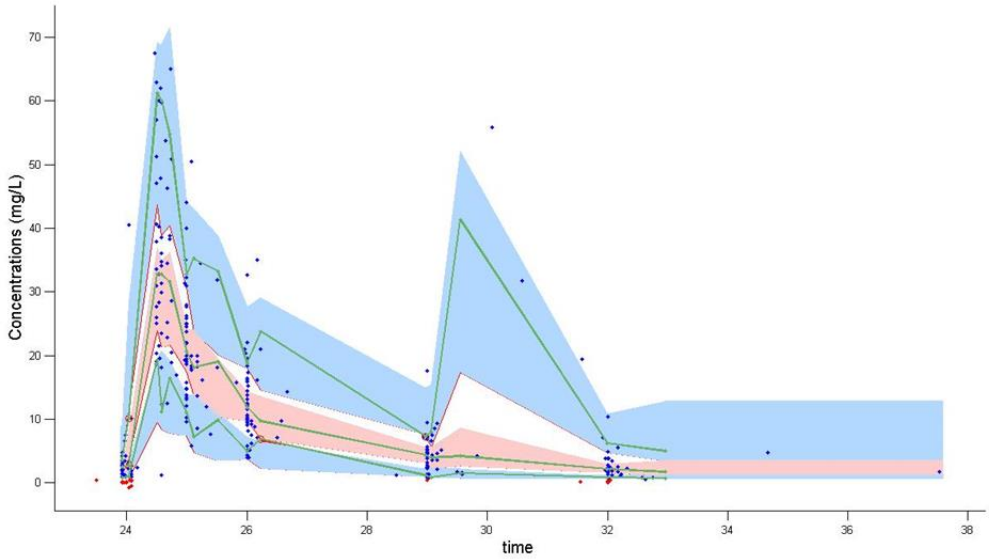

(a)
Observations
Population predictions
(c)
Observations
Individual predictions
(b)
PWRES
Populations predictions
(d)
IWRES
Individual predictions

Figure 3

(a)


Concentrations (mg/L)
70
60
50
40
30
20
10
0
24
26
28
30
32
34
36
38
time

(b)

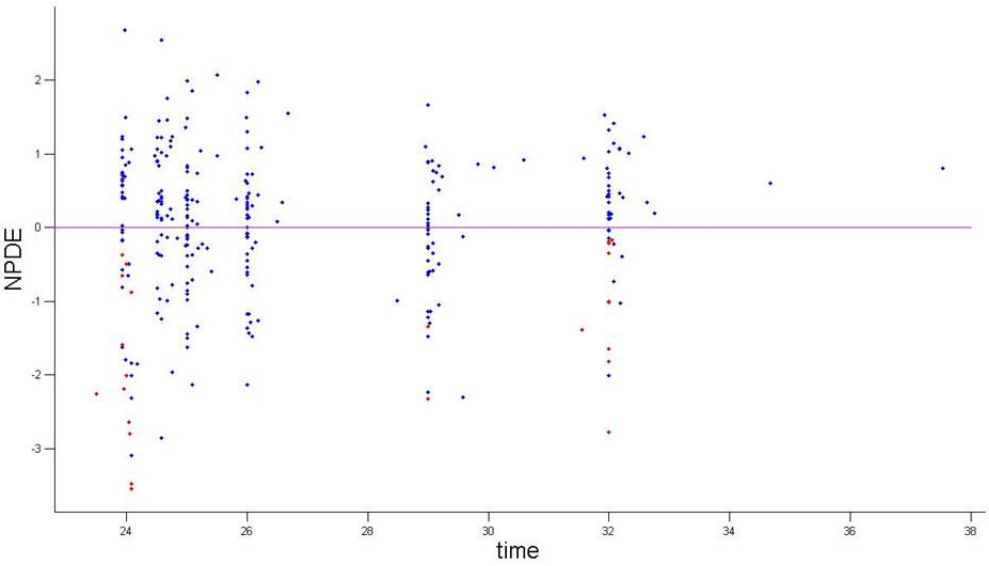

NPDE
2
1
0
-1
-2
-3
24
26
28
30
32
34
36
38
time

Figure 4

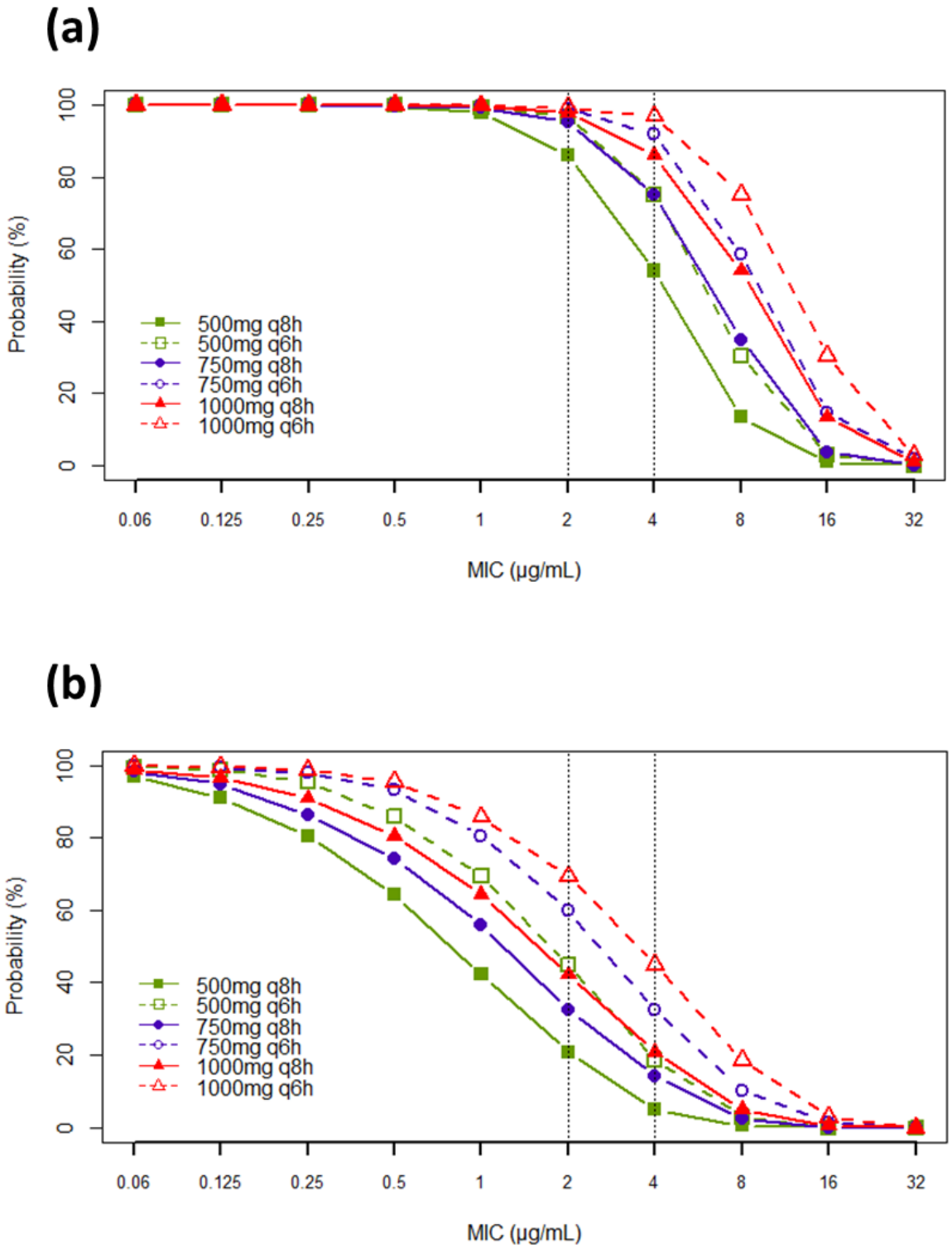

(a)
Probability (%)
0
20
40
60
80
100
500mg q8h
500mg q6h
750mg q8h
750mg q6h
1000mg q8h
1000mg q6h
0.06
0.125
0.25
0.5
1
2
4
8
16
32
MIC (µg/mL)
(b)
Probability (%)
0
20
40
60
80
100
500mg q8h
500mg q6h
750mg q8h
750mg q6h
1000mg q8h
1000mg q6h
0.06
0.125
0.25
0.5
1
2
4
8
16
32
MIC (µg/mL)

Figure 5

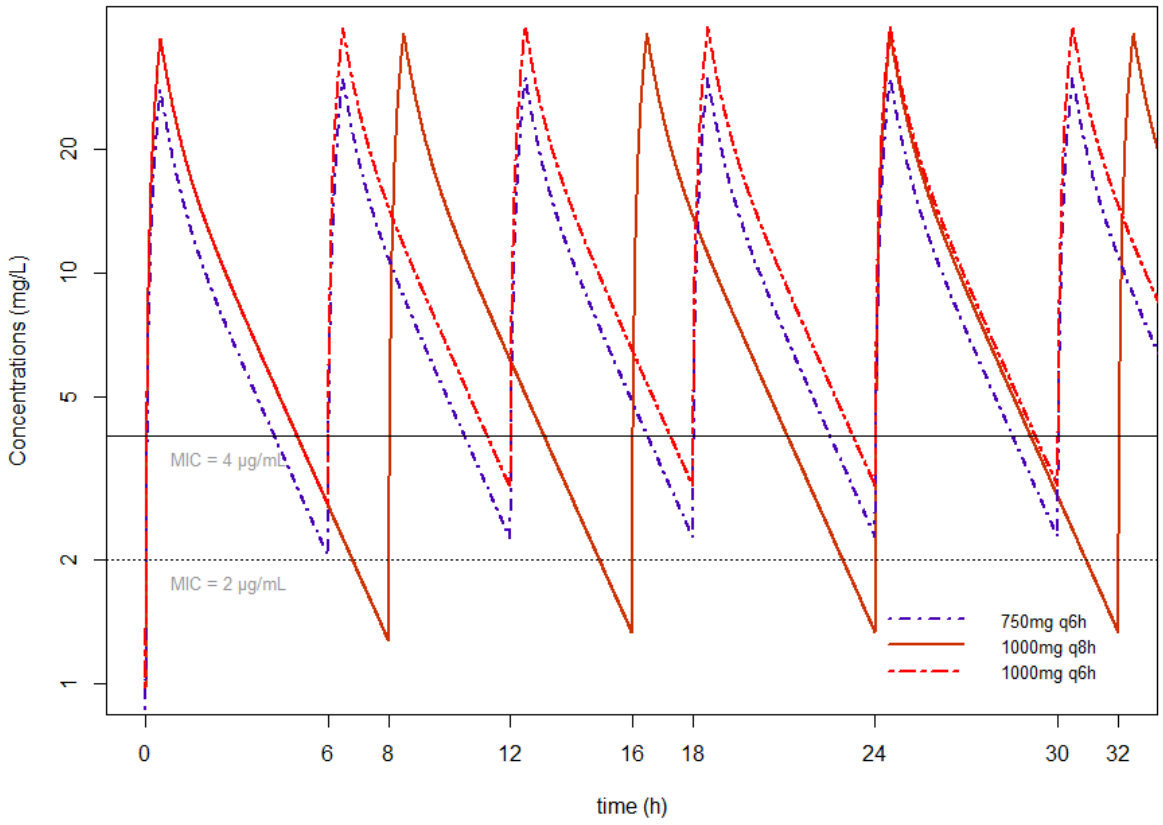

Concentrations (mg/L)
1
2
5
10
20
MIC = 4 µg/mL
MIC = 2 µg/mL
750mg q6h
1000mg q8h
1000mg q6h
0
6
8
12
16
18
24
30
32
time (h)

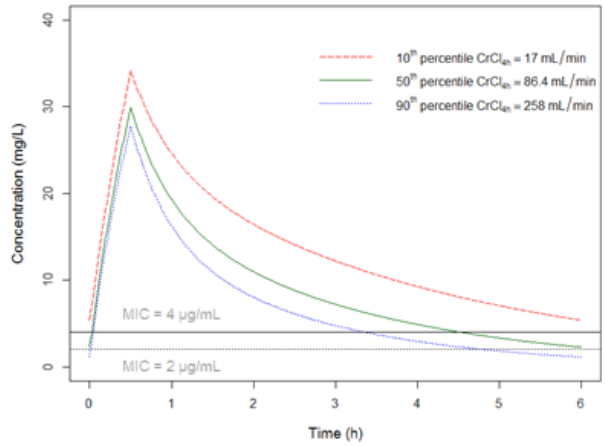
Figure 6

Table S1: Expected fractional time above MIC (fT > MIC) for two target MICs 2 and 4 µg/mL for 1000 mg q8h and 750 mg q6h dosage regimen and population parameters for the 10th, 50th and 90th percentiles of the three significant covariates.

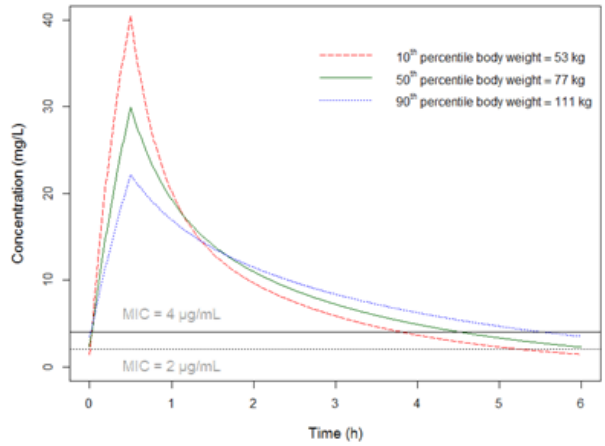
1000 mg q8h	MIC = 2 µg/mL			MIC = 4 µg/mL		
	10th	50th	90th	10th	50th	90th
$CrCl_{4h}$*	100	86.5	66.5	97.2	63.7	48.1
Body weight**	72.7	86.5	100.0	53	63.7	77.4
Serum albumin***	100.0	86.5	78.0	80.0	63.7	57.7
750 mg q6h	MIC = 2 µg/mL			MIC = 4 µg/mL		
	10th	50th	90th	10th	50th	90th
$CrCl_{4h}$*	100	100	79.9	100	74.8	55.2
Body weight**	88.0	100	100	63.1	74.9	92.0
Serum albumin***	100	100	94.7	95.3	74.9	67.7

* 10th = 17 mL/min; 50th = 86.4 mL/min and 90th = 258 mL/min
** 10th = 53 kg; 50th = 77 kg and 90th = 111 kg
*** 10th = 11 g/L; 50th = 18 g/L and 90th = 23 g/L

(a)



(b)



(c)

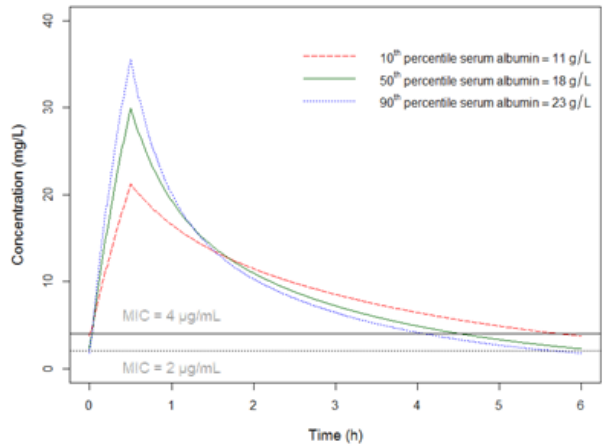


Figure S1 : Predicted steady-state concentrations of imipenem for 750 mg q6h dosage regimen with percentile values (10th, 50th and 90th) of the three significant covariates:
With (a) Creatinine clearance percentiles: 10th = 17 mL/min; 50th = 86.4 mL/min; 90th = 258 mL/min
(b) Body weight: 10th = 53 kg; 50th = 77 kg; 90th = 111 kg
(c) Serum albumin: 10th = 11 g/L; 50th = 18 g/L; 90th = 23 g/L
Vertical lines are displayed for MIC = 2 µg/mL and MIC = 4 µg/mL.