Journal of Antimicrobial Chemotherapy

Dosing strategies of imipenem in neonates based on pharmacometric modelling and simulation

Kim Dao [1]*†, Aline Fuchs[1]†, Pascal André[1], Eric Giannoni[2], Laurent A. Decosterd [3], Oscar Marchetti[4,5], Sandra A. Asner[6], Marc Pfister[7], Nicolas Widmer [1,8,9], Thierry Buclin[1], Chantal Csajka [9,10,11] and Monia Guidi[1,9,10]

[1]*Service of Clinical Pharmacology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland;* [2]*Clinic of Neonatology, Department Mother-Woman-Child, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland;* [3]*Innovation and Development Laboratory, Service of Clinical Pharmacology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland;* [4]*Service of Infectious Disease, Department of Medicine, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland;* [5]*Department of Medicine, Ensemble Hospitalier de la Côte, Morges, Switzerland;* [6]*Pediatric Infectious Disease and Vaccinology Unit, Department Mother-Woman-Child, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland;* [7]*Pediatric Pharmacology and Pharmacometrics, University of Basel Children's Hospital, UKBB, Basel, Switzerland;* [8]*Pharmacy of the Eastern Vaud Hospitals, Rennaz, Switzerland;* [9]*Institute of Pharmaceutical Sciences of Western Switzerland, University of Geneva, University of Lausanne, Geneva, Lausanne, Switzerland;* [10]*Center for Research and Innovation in Clinical Pharmaceutical Sciences, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland;* [11]*School of Pharmaceutical Sciences, University of Geneva, Geneva, Switzerland*

*Corresponding author. Email: kim.dao@chuv.ch
†These authors contributed equally to this work.

Objectives: Imipenem is a broad-spectrum antibacterial agent used in critically ill neonates after failure of first-line treatments. Few studies have described imipenem disposition in this population. The objectives of our study were: (i) to characterize imipenem population pharmacokinetics (PK) in a cohort of neonates; and (ii) to conduct model-based simulations to evaluate the performance of six different dosing regimens aiming at optimizing PK target attainment.

Methods: A total of 173 plasma samples from 82 neonates were collected over 15 years at the Lausanne University Hospital, Switzerland. The majority of study subjects were preterm neonates with a median gestational age (GA) of 27 weeks (range: 24–41), a postnatal age (PNA) of 21 days (2–153) and a body weight (BW) of 1.16 kg (0.5–4.1). PK data were analysed using non-linear mixed-effect modelling (NONMEM).

Results: A one-compartment model best characterized imipenem disposition. Population PK parameters estimates of CL and volume of distribution were 0.21 L/h and 0.73 L, with an interpatient variability (CV%) of 20.1% on CL in a representative neonate (GA 27 weeks, PNA 21 days, BW 1.16 kg, serum creatinine, SCr 46.6 μmol/L). GA and PNA exhibited the greatest impact on PK parameters, followed by SCr. These covariates explained 36% and 15% of interindividual variability in CL, respectively.

Simulated regimens using a dose of 20–25 mg/kg every 6–12 h according to postnatal age led to the highest PTA (*T*>MIC over 100% of time).

Conclusions: Dosing adjustment according to BW, GA and PNA optimizes imipenem exposure in neonates.

Introduction

Imipenem is a broad-spectrum carbapenem antibiotic with bactericidal activity against numerous Gram-positive, Gram-negative and anaerobic microorganisms. It is used to treat severe and complex bacterial infections caused by resistant or multiple organisms in critically ill patients, including neonates.[1–4] Although imipenem dosing and pharmacokinetics (PK) are well established in infants older than 3 months and in adults, with or without renal impairment,[5] few studies have evaluated the PK of imipenem in neonates.[6–11] A unique published neonatal population PK model, including patients with a gestational age of 30 to 41 weeks, describes the influence of body weight on imipenem CL.[11] Considering that imipenem is hydrophilic, little bound to plasma

proteins (∼20%), and predominantly eliminated by the kidneys, accurate characterization of the impact of maturational changes in kidney function is key to developing efficacious and safe dosing strategies in neonates.[12,13]

In the USA, imipenem (Primaxin®) is approved by the FDA for treatment of neonates weighing >1.5 kg. The label recommends giving 25 mg/kg every 12 h in neonates younger than 1 week of age and every 8 h for those aged between 1 and 4 weeks. It is used *off-label* for bacterial sepsis according to European, Swiss and Japanese authorities, and dosing strategies are lacking for very low birth weight preterm neonates.[14]

To fill these gaps in knowledge, the objectives of this pharmacometric study were: (i) to characterize the population PK of imipenem in a large cohort of neonates; and define clinical and demographic factors that might influence imipenem disposition in preterm and term neonates; (ii) to perform pharmacometric simulations comparing existing imipenem dosing regimens with respect to a target attainment of 100% of the T>MIC.[15]

Patients and methods

Study population

Our study retrospectively included all infants hospitalized in the neonatal intensive care unit (NICU) of Lausanne University Hospital, Switzerland between 2002 and 2017 treated with imipenem/cilastatin for suspected or proven infection (i.e. positive cultures), who had at least one measurement of the imipenem concentration in plasma. For each patient, information regarding sampling time and dosing history of imipenem was extracted from clinical charts. Patients with missing information regarding drug administration were excluded. The following clinical and demographic characteristics were collected: gender, bodyweight at birth (bBW), bodyweight at sampling time (BW), gestational age (GA), postnatal age (PNA), small for gestational age (SGA), serum creatinine (SCr), concomitant treatment with furosemide, spironolactone, hydrochlorothiazide, vancomycin, metronidazole and erythromycin. Postmenstrual age (PMA) was defined as the sum of GA and PNA.

Imipenem concentrations were extracted from the institutional therapeutic drug monitoring (TDM) database before 2006 and from the NICU clinical information system (MetaVision®, iMDsoft, Massachussetts, USA) since 2006. Cilastatin concentrations were measured only since 2013. Imipenem co-formulated with cilastatin (either Tienam®, MSD Merck Sharp & Dohme AG, Lucerne, Switzerland or Imipenem-Cilastatine Labatec, Geneva, Switzerland) was always administered intravenously as a 30 min infusion, using an infusion pump. Initial imipenem dosage was 15–20 mg/kg every 8–12 h according to BW and PNA, with further dose adjustment guided by TDM. Given wide interindividual variations in the pharmacokinetics of imipenem in critically ill children (including neonates), TDM was often requested to optimize treatment on an individual basis.[16] Plasma samples were drawn at the discretion of NICU physicians either at C_{max} (1–2 h after infusion start), at C_{min} (under steady-state conditions, before the fourth dose in general) or both. A $C_{min} \geq 2$ mg/L was targeted in the absence of a defined MIC. Individualized dosing was then adjusted based on joint recommendations of consultants in clinical pharmacology and infectious diseases.

In neonates with missing value of SCr on the day of sampling for imipenem concentration measurement, an SCr value was calculated using linear interpolation between the two closest known adjacent values (in three patients, interpolation was not possible and the SCr value of the previous day was used).[17] This retrospective study was approved by the research ethics committee of the canton of Vaud (CER-VD, protocol authorization 100/07, 10 May 2007).

Analytical assays

From 2002 to 2009, free imipenem plasma concentration was measured by an HPLC method,[16] validated according to FDA recommendations. The calibration curve was linear from 0.5–200 mg/L with inter-run and intra-run coefficients of variation <13.4% (at 4, 40, 120 mg/L) and <6%, respectively.[18] From July 2009 onwards, total plasma imipenem concentrations were quantified by LC-MS/MS.[19] The calibration curve was linear in the concentration range of 0.1–100 mg/L and the method was precise [inter-day coefficient of variation (CV) <7%] and accurate (bias <2%) with a lower limit of quantification (LLOQ) of 0.1 mg/L. Cilastatin concentration was measured by LC-MS/MS since 2013. SCr measurement was performed using the modified Jaffe Gen 2 compensated method (Cobas 8000 analyser, Roche Diagnostics, Rotkreuz, Switzerland) standardized according to IDMS-traceable method.

Pharmacometric modelling to characterize population PK in neonates

Base model

A population PK analysis was performed using a non-linear mixed effect modelling approach (NONMEM®, version 7.3, ICON Development Solutions, Ellicott City, MD, USA). Free and total plasma imipenem concentration values were analysed together, considering that imipenem has a very low fraction of plasma protein binding (∼20% in adults), that binding affinity is reduced in neonates[20] and that free and total concentration values were within the same range of concentrations in our dataset. A stepwise procedure was used to identify the model that best fitted the data. One-, two- and three-compartment models were compared with linear and non-linear elimination. We directly included BW in the model because of its reported relevance in neonates. The influence of BW on PK parameters was quantified using an allometric model defined as $P = \theta_1 \cdot (BW/BW_{med})^{PWR}$, where θ_1 is the typical value of the parameter P, and PWR was set to 0.75 for clearances and 1 for volumes of distribution.[21] Inter-patient variability was sequentially assigned to PK parameters and several error models were tested to describe the residual unexplained variability. Potential biases related to both methods measuring free and total imipenem concentrations were evaluated by integration of the analytical method effect on the error model. Cilastatin concentrations were not analysed due to a large amount of missing data.

Covariate model

The rationale for inclusion of covariates was based: (i) on common developmental PK knowledge[20,22] as basis for the inclusion of age in the model building, as well as (ii) graphical exploration of available covariates for correlation with individual PK parameter estimates. GA, PNA, PMA, SGA, SCr as a measure for kidney function, concomitant treatments potentially impacting imipenem elimination (furosemide, spironolactone, hydrochlorothiazide, vancomycin, metronidazole and erythromycin) and gender were included in the model, following sequential forward selection and backward elimination procedures. Continuous covariates were tested for their potential influence on PK using linear, exponential and power models as appropriate. PMA was also tested with a maturation function (Hill equation).[23,24] SGA, gender, concomitant treatments and analytical methods were evaluated as categorical covariates.

Model selection and parameter estimation

Model estimation was performed using the first-order conditional estimation with interaction (FOCE-I). Imipenem concentration measurements below the LLOQ were handled with the M6 method and replaced by LLOQ/2.[25] The M3 method did not increase overall model performance. As a goodness-of-fit statistic, NONMEM® computes an objective function value (OF). The likelihood ratio test, based on the difference in objective function

values (ΔOF) between two nested models, was used to compare them. A ΔOF was considered statistically significant if it exceeded 3.8 ($P < 0.05$) and 6.6 ($P < 0.01$) points for one additional parameter during model-building and backward deletion procedures, respectively. Model assessment was also based on goodness-of-fit plots, along with precision of the PK parameters estimations. A sensitivity analysis was also performed for patients with absolute values for conditional weighted residuals (|CWRES|) >3.[26,27]

Model evaluation

The final model stability was assessed by the bootstrap method as implemented in the PsN-Toolkit[28] (version 3.5.3, Uppsala University, Uppsala, Sweden). The median and 95% CI estimated from 2000 re-sampled datasets were compared with the original model estimations. In addition, prediction-corrected visual predictive checks (pcVPC)[29] were performed with PsN-Toolkit and Xpose4[30] (version 4.3.5, Uppsala University, Uppsala, Sweden) by simulations based on the final PK estimates using 2000 individuals. Mean prediction-corrected concentrations with their 95% percentile interval (95% PI) at each timepoint were retrieved. Plots were generated using R (version 2.15.1, R Development Core Team, Foundation for Statistical Computing, Vienna, Austria).

Pharmacometric simulation to evaluate dosing regimens in neonates

We compared six different imipenem dosing regimens reported for neonates in the literature (Table 1) through model-based simulations. The *in vivo* efficacy of carbapenems, as with other β-lactam antibiotics, is best predicted by the proportion of the dosing interval during which plasma drug concentrations are above the MIC (T>MIC) for the causative microorganism. A variable range of T>MIC is reported for optimal antibacterial efficacy, between 40%[1,3,31] and 100%, in particular in critically ill patients with

life-threatening infections (such as preterm neonates with an immature immune system).[15,32–34] The clinical breakpoint for imipenem susceptibility in the majority of bacteria according to the EUCAST criteria is 2 mg/L.[35]

The final population PK model for imipenem was applied to the original dataset to predict the PTA in terms of T>MIC of total imipenem concentrations over 1 and 7 day(s) of treatment for each dosing regimen. Total concentrations were used for simulations. The PTA was computed considering cut-offs of 40%, 60%, 80% and 100% of T>MIC. No upper threshold for toxicity was evaluated since a clear concentration–toxicity relationship is not described for imipenem in the literature.

Results

Study data

Demographic characteristics of the study population, which included mostly preterm neonates ($n = 73$, 89%), are presented in Table 2. Two samples were excluded due to collection bias. Dosing intervals were initially of 8 or 12 h and then ranged from 4–28 h. No neurological adverse reactions, or overdosing related to imipenem were reported.

Pharmacometric modelling to characterize population PK of imipenem in neonates

Base model

A one-compartment open model, parameterized in terms of CL and volume of distribution (V), best described our data. Although significant model improvement was observed with a two-compartment model (ΔOF=−40.2, $P < 0.001$), intercompartmental

Table 1. Evaluated dosing regimens for imipenem

Reference	GA (weeks)	PNA (days)	Weight (kg)	Dose (mg/kg)	Interval (h)
FDA[14]		<7		25	12
		≥7		25	8
		≥28		25	6
NNF 7[59]		<7		20	12
		≥7		20	8
		≥28		20	6
BNFC 2016–17[60]		<7		20	12
		≥7		20	8
		≥21		20	6
Neofax 2014[61]				25	12
Redbook 2012[62]		≤7	≤2	20	12
		>7	≤2	25	12
		≤7	>2	25	12
		>7	>2	25	8
NICU-Lausanne	≤29	≤14		20	12
	≤29	>14		25	12
	29–35	≤7		20	12
	29–35	7–14		25	12
	29–35	>14		25	8
	≥35	≤7		25	12
	≥35	>7		25	8

PNA, postnatal age (weeks); GA, gestational age (weeks); FDA, product label information according to the FDA; NNF 7, Neonatal Formulary, 7th Edn; BNFC, British National Formulary for Children.

Table 2. Demographics and clinical characteristics of neonates at the time of first imipenem concentration measurement

Characteristics	Median (range) or count (%)
Patients (*n* = 82)	
Gender (male/female)	38 (46%)/44 (54%)
Gestational age (weeks)	26.9 (24.2–41.3)
Postnatal age (days)	21 (2.1–153)
Postmenstrual age (weeks)[a]	31.0 (25.6–48.3)
Bodyweight (g)	1155 (500–4120)
Plasma creatinine (μmol/L)	46.6 (9–243)
Concentrations (*n* = 173)	
Imipenem dose (mg/kg)	20 (10–38)
Below the limit of quantification	7 (4%)
Number of C_{min} values	128 (74%)
C_{min} (mg/L)	1.4 (0.1–12.0)
C_{max} (mg/L)	24.2 (7.7–63.7)
Concentrations per patient	2 (1–8)
Medications[b]	
Furosemide	20 (36%)
Spironolactone	3 (4%)
Hydrochlorothiazide	5 (7%)
Vancomycin	41 (82%)
Metronidazole	12 (19%)
Erythromycin	3 (4%)

[a]Postmenstrual age (weeks) is defined as the sum of gestational age and postnatal age.
[b]Only relevant medications have been searched; count on total concentration measurements.

CL and peripheral V were poorly estimated: the two-compartment model was therefore not considered for further analysis. Interindividual variability was assigned to CL, while adding further variability on V did not improve the model (ΔOF=−0.1, *P* > 0.5). Residual unexplained variability (RUV) was best described by a mixed residual error model, without a detected distinction between total and free concentrations (ΔOF=+0.5, *P* > 0.5). The incorporation of BW on CL and V using the appropriate allometric functions markedly improved the description of the data (ΔOF=−70.3, *P* < 0.001) while explaining 9% of the interindividual variability on CL. The final allometric base population parameters with interindividual variability (CV%) were a CL of 0.25 L/h (37.4%) and a V of 0.69 L for a neonate of median BW. RUV was 34% and 0.31 mg/L for the proportional and additional error components, respectively. The effect of analytical methods on residual error was non-significant.

Covariate model

In the univariate analysis, inclusion of PNA and GA using linear relationships significantly improved the model (ΔOF=−46.1 and −18.9, respectively, *P* < 0.001). The inclusion of SCr (ΔOF=−51.3, *P* < 0.001) and of concomitant use of diuretics on CL (ΔOF=−16.6, *P* < 0.001), also significantly improved the model. The other tested covariates (SGA, albumin and concomitant medications) had no significant effect on imipenem CL (ΔOF < 1, *P* > 0.5). In the multivariate analysis, the age dependency of CL was best captured by a linear relationship combining PNA and GA, which together explained 36% of the interindividual variability on CL and SCr further explained 15% of the remaining interpatient variability.[36] A sigmoid maturation function (MF), calculated as MF = (PMA^{HILL})/(PMA^{HILL} + T$_{50}^{HILL}$), where T$_{50}$ represents the PMA when 50% of maturation of CL has been reached and HILL the Hill coefficient (the slope of the sigmoid model), failed to better describe the data.[37] The effect of diuretics was lost in the multivariate analysis in favour of SCr (ΔOF = 0 compared with the model with SCr alone, *P* > 0.5). A summary of the major steps of the multivariate analysis is given in Table S1 (available as Supplementary data at *JAC* Online). The extent of η-shrinkage was 8% in the final model, which included BW, PNA, GA and SCr as covariates. The model described the observed data well, as indicated by the goodness-of-fit plots in Figure S1. According to the final model, a term neonate (GA 40 weeks, PNA 3 weeks, BW 3.1 kg, SCr 46 μmol/L) would have a CL of 0.73 L/h, while a very preterm neonate (GA 24 weeks, PNA 3 weeks, BW 0.52 kg, SCr 46 μmol/L) would have a CL of 0.10 L/h. This means that CL is expected to be 86% lower in extremely preterm neonate, compared with a term neonate. In a representative neonate of our study population (GA 27 weeks, PNA 21 days, BW 1.16 kg, SCr 46.6 μmol/L) for whom the estimated CL is 0.22 L/h, the terminal half-life of imipenem would be 2.4 h. In the same neonate having renal failure (SCr 200 μmol/L), a 25% reduction in imipenem CL (0.16 L/h) is expected.

Model evaluation

Table 3 presents the median parameter estimates obtained with the bootstraps with the 95% CI, which were in agreement with the parameters of the final population pharmacokinetic model. A sensitivity analysis regarding two data points with |CWRES| > 3 showed that none of these concentrations affected the pharmacokinetic estimates with a maximum difference in parameter estimates of 8% for the creatinine factor (data not shown). The impact of one patient that received treatment during the first 3 days of life was also insignificant. The results of pcVPC (Figure 1) supported the predictive performance of the model up to 12 h post-dose. The model was less predictive beyond 12 h post-dose, which is attributable to the few observations collected more than 12 h after drug administration. The model was however judged acceptable, since imipenem dosing intervals are either equal or shorter than 12 h.

Pharmacometric simulations to evaluate dosing regimens in neonates

The results of simulations performed with six different dosing regimens are summarized in Figure 2 and Table S2. Total imipenem concentrations were used for simulations, as there were no significant differences between methods measuring free and total imipenem concentrations. Our model predicts a non-significant 5% (precision ±19%) difference between free and total concentrations, suggesting that protein binding in neonates might be lower than 20%. Model-based simulations indicate that only the FDA, NNF 7 and BNFC regimens were successful in maintaining imipenem concentrations above an MIC of 2 mg/L in most patients for 100% of the time interval between the doses on days 1 and 7. The most intensive regimen registered by the FDA, giving 25 mg/kg every 12, 8 and 6 h according to PNA, reached the highest PTA of

Table 3. Estimated population pharmacokinetic parameters and bootstrap 95% CI

Parameters (units)	Parameters	Final parameter estimates (RSE%)	Bootstrap model estimates (95% CI)
CL (L/h)	θ_{CL}	0.21 (6)	0.21 (0.19–0.23)
Allometric power of BW on CL		0.75	0.75
Effect of PNA on CL	θ_{PNA}	0.22 (19)	0.22 (0.13–0.32)
Effect of GA on CL	θ_{GA}	1.31 (20)	1.33 (0.83–1.92)
Effect of SCr on CL	θ_{SCr}	0.20 (26)	0.19 (0.06–0.29)
V (L)	θ_V	0.73 (7)	0.72 (0.63–0.83)
Allometric power of BW on V		1	1
Proportional error (% CV)	θ_6	37 (7)	37 (31–41)
Additive error (mg/L)	θ_7	0.04 (12)	0.04 (0.03–0.15)
IIV CL (% CV)	ω_1	20 (12)	19 (15–24)

CL, total clearance; BW, actual bodyweight (kg); PNA, postnatal age (weeks); GA, gestational age (weeks); SCr, plasma creatinine (μmol/L); V, volume of distribution; IIV, inter-individual variability.
Final model:

$$CL = \theta_{CL} \cdot \left(\frac{BW}{BW_{med}} \right)^{0.75} \cdot \left(1 + \theta_{PNA} \cdot \frac{PNA - PNA_{med}}{PNA_{med}} \right) \cdot \left(1 + \theta_{GA} \cdot \frac{GA - GA_{med}}{GA_{med}} \right) \cdot \left(\frac{SCr_{med}}{SCr} \right)^{\theta_{SCr}}$$

$$V = \theta_V \cdot \left(\frac{BW}{BW_{med}} \right)^{0.75}$$

Which means that for a patient of 2.0 kg, PNA 2 weeks, GA 32 weeks, SCr 40 μmol/L, imipenem CL is 0.38 L/h. For instance, the influence of an increase of 1 kg on CL will be: +0.14 L/h (CL: 0.52 L/h), an increase in 1 week of PNA on CL: +0.3 L/h (CL: 0.41 L/h), an increase in 1 week of GA on CL: +0.1 L/h (CL: 0.39 L/h) and an increase of 50 μmol/L of SCr on CL: −0.6 L/h (CL: 0.32 L/h).
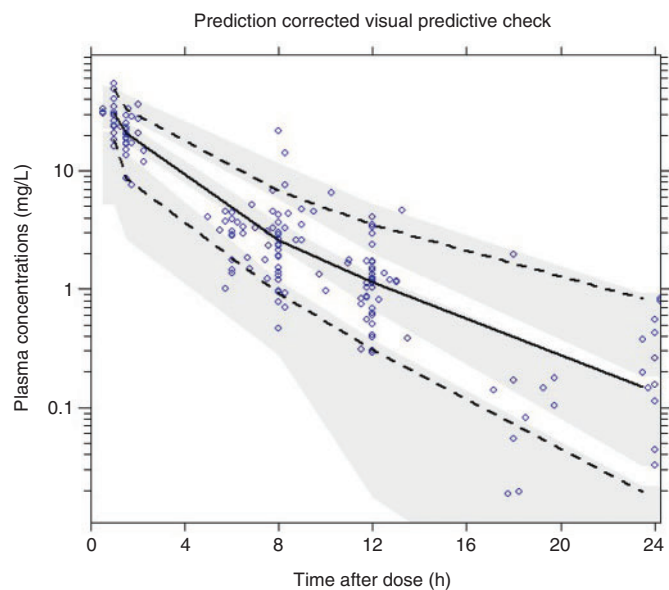

Prediction corrected visual predictive check

Figure 1. Prediction-corrected visual predictive check of the final model with imipenem prediction-corrected concentrations (circles) and median observations (solid line) with the corresponding 90% observation interval (dotted lines). Grey-shaded areas represent the model-based percentile 95% CI. Observed and simulated concentrations are based on the typical population prediction for the median independent variable. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

85% and 83% on days 1 and 7, respectively. Neofax, Redbook and NICU-Lausanne regimens achieved much lower PTA on days 1 and 7. Considering a higher MIC of 4 mg/L, FDA, NNF 7 and BNFC regimens achieved a PTA of 48%, 29% and 38% on day 1, and 43%, 28% and 35% on day 7. Neofax, Redbook and NICU-Lausanne regimens were clearly suboptimal in such situations (PTA of 0%–2%).

Discussion

This study provides the first pharmacometric analysis of imipenem performed in a large cohort of preterm and term neonates, including critically ill patients. Significant covariates influencing imipenem disposition such as BW, age and kidney function were identified.[38] The knowledge of their influence on imipenem disposition will contribute to inform initial dose adjustment for optimizing antibacterial exposure of imipenem in this population.

A one-compartment open model with first-order elimination best described our data. As expected and already described,[11] actual BW implemented using an allometric exponent is a major covariate. The allometric exponent accounts for a progressive increase in imipenem CL and V along with BW, a surrogate of body size.[21,39] Inclusion of age parameters (GA and PNA) had the most significant effect in explaining interpatient variability in CL. A maturation function (sigmoid E_{max} function), often preferred to describe physiological changes occurring in the first weeks of life, failed to better describe our data, compared with a linear function. The median timing of administration of 3 weeks of life, when major
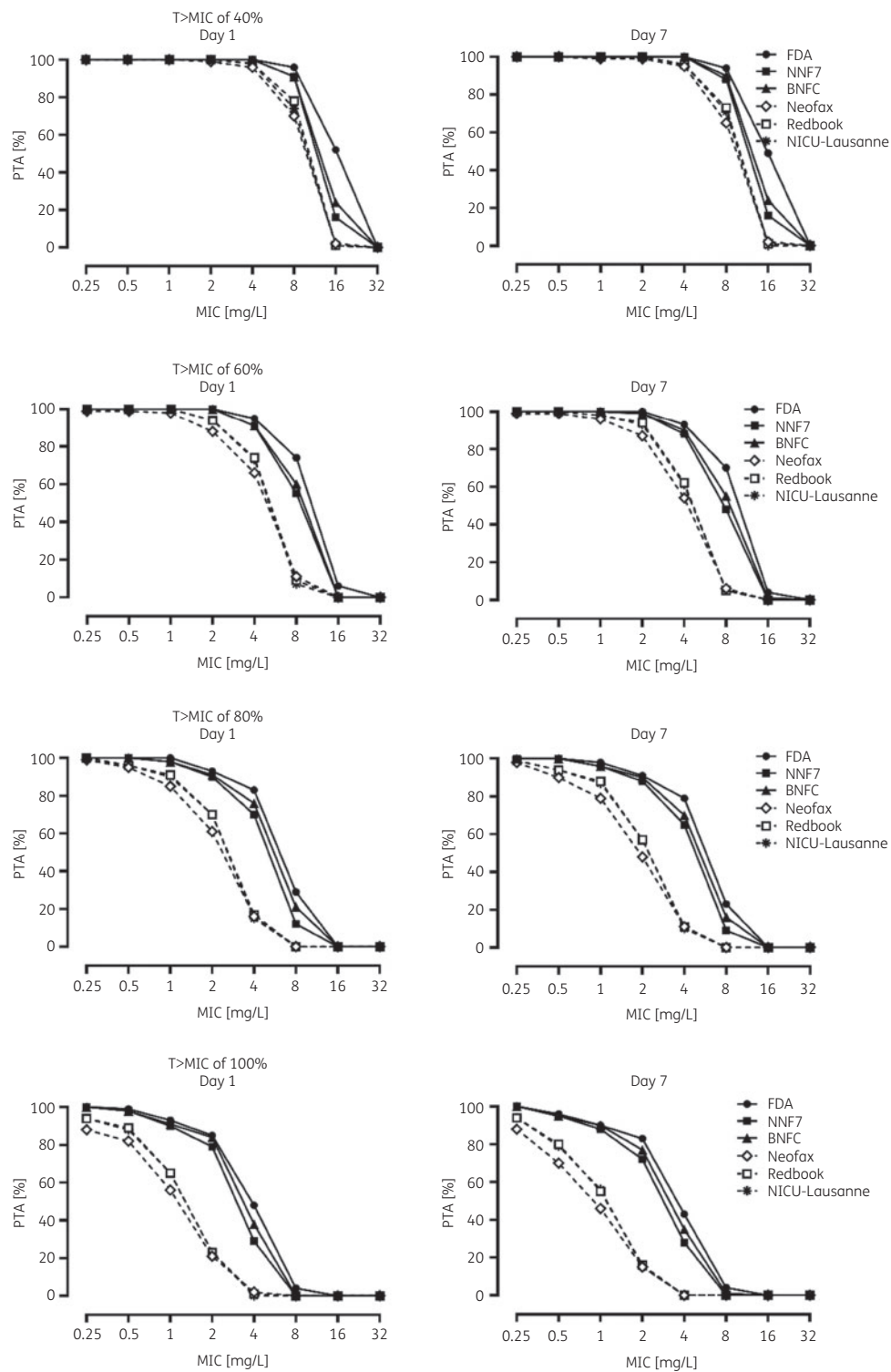
Figure 2. PTA according to different values of MIC for each simulated regimens on day 1 (left) and day 7 (right) for cut-offs of *T*>MIC ranging from 40 to 100%.

postnatal changes in CL and V have already occurred, may explain these results. As expected, the inclusion of SCr inversely influenced CL and further improved the model. Although SCr is generally a good predictor of glomerular filtration rate in adults, it is less reliable in very preterm neonates due to differences in muscle mass, age or length compared with older infants.[40,41] No better means to estimate kidney function were however available in this study. An indication bias probably explains why diuretic use

JAC

improved the model in the univariate analysis, but not in the multivariate analysis. Other tested covariates (co-medications, SGA) did not show a relevant impact on imipenem disposition. No significant difference was found when analytical methods were evaluated; suggesting that protein binding of imipenem is very low (as methods respectively measured either free or total concentrations), which is in accordance with the fact that free and total concentration values were within the same range of concentrations in our dataset.

A previous population PK study failed to describe the age dependency of imipenem CL, probably due to a limited number of included very preterm neonates and the absence of extremely preterm neonates.[11] Our study confirms that the half-life of imipenem is longer in younger neonates, due to immature organ function (reduced CL) and a larger V. The V of imipenem would average 0.75 L for a representative preterm patient (GA 27 weeks, PNA 3 weeks, BW 1.2 kg) versus 1.95 L for a term neonate. This corresponds to a 26% longer half-life of 2.4 h for a preterm versus 1.9 h for a term neonate. Since imipenem is a hydrophilic and polar compound, predominantly distributed into intra- and extravascular compartments, a larger V is likely a consequence of the large extracellular content of water in neonates.[12] In addition, sepsis may have contributed to an increased capillary permeability linked to the inflammatory response, resulting in a larger extravascular distribution.[42] V is larger in neonates (0.63 L/kg) compared with older children and adults (0.46 L/kg for a 3 year-old patient,[16] 0.26 L/kg for a 9 year-old one[11] and about 0.22 L/kg for adult patients[43–47]) and imipenem half-life ranges from 0.5–1.2 h[11,48] and 1–3 h[43–47,49–52] for older children and adults, respectively.

Imipenem is recommended for the treatment of infections due to Gram-negative bacilli resistant to cephalosporins (typically those possessing an extended spectrum β-lactamase) or as a second line treatment for sepsis or septic shock.[12] Rapid target attainment in life-threatening infections is paramount considering that most patients receiving imipenem are critically ill and likely to have been previously treated unsuccessfully with other antibiotics. Pharmacometric simulations suggested that the dosing regimens of the FDA, NNF 7 and BNFC ensured the highest PTA on day 1 and 7 with a weight-adjusted dose ranging from of 20–25 mg/kg and dosing intervals of 6–12 h (based on PNA). The regimen of the FDA performed best to maintain total imipenem concentrations at 100% of T>MIC in a majority of the neonates for MIC values up to 2 mg/L, the clinical breakpoint for imipenem susceptibility according to EUCAST.[53] Considering a higher MIC of 4 mg/L, all the evaluated regimens were suboptimal, especially the Neofax, Redbook and NICU-Lausanne regimens. Considering lower cut-offs of PTA of 40% of the T>MIC, as suggested by some authors,[1,3,31] all six regimens could provide adequate exposure for MIC up to 4–8 mg/L.[15] Of note, similar single doses of 20–25 mg/kg are used in all six regimens, with different dosing intervals. A dose of 20 mg/kg is sufficient to maintain a T>MIC over 100% in all patients if the MIC is <2 mg/L. A higher dose of 25 mg/kg or prolonged infusions may be of interest for treating microorganisms with higher MICs.[54] Shorter dosing intervals of 6 h and 8 h for neonates with a PNA >21 days and >7 days, respectively (as supported by the FDA, NNF 7 and BNFC) appear to be more adequate than other guidelines in terms of PTA. Adjustment of dosing according to GA and PNA (as recommended in NICU-Lausanne) does not bring any additional value, probably because GA is already largely correlated to BW and that physiological changes are majorly guided by postnatal changes.

Safety concerns such as seizures or toxic encephalopathy, a serious dose-dependent adverse effect of imipenem[55–57] in patients with renal failure, were not investigated in this study. Unfortunately, sufficient cilastatin concentrations were not available to develop a model for cilastatin, which would have been of interest because cilastatin plasma CL is 20%–30% of that of imipenem. As this study could not investigate the accumulation of cilastatin in neonates, the need for an adapted imipenem:cilastatin ratio for neonates remains unclear.[6]

The main limitation of this study is the retrospective design, fostering potential bias during recollection of information. Imipenem concentrations were measured as part of routine clinical care and only sparse samples were available, our data were therefore insufficient to describe a two-compartment model. However, in accordance with our results, a one-compartment model was also reported in the only other published population PK study of imipenem in neonates.[11] The lack of external validation of our model and prospective validation of the different dosing regimens regarding antibacterial efficacy and safety of imipenem therapy are other limitations.

In conclusion, the present study describes the first detailed population PK model of imipenem in a cohort of predominantly preterm neonates. Inter-subject variability of imipenem concentrations is mostly explained by expected physiologic and pathologic variables (BW, GA, PNA and kidney function). This model was applied to simulate concentration–time profiles for various dosing regimens in order to determine the best a priori dosing recommendations. Using FDA, NNF 7 or BNFC regimens appears on this basis commendable, along with TDM whenever possible to better individualize imipenem dosages, in particular during prolonged treatment. The next steps will include the external validation of the model and the implementation of the developed model in Tucuxi (HEIG-VD, Yverdon, Switzerland), a Bayesian computer tool for dose individualization based on a single blood concentration measurement, in neonates[58] and prospective clinical studies to confirm these results.

Transparency declarations

None to declare.

Supplementary data

Figure S1 and Tables S1 and S2 are available as Supplementary data at *JAC* Online.

References

1 Zhanel GG, Wiebe R, Dilay L *et al.* Comparative review of the carbapenems. *Drugs* 2007; **67**: 1027–52.

2 Gray JW, Patel M. Management of antibiotic-resistant infection in the newborn. *Arch Dis Child Educ Pract Ed* 2011; **96**: 122–7.

3 de Hoog M, Mouton JW, van den Anker JN. New dosing strategies for antibacterial agents in the neonate. *Semin Fetal Neonatal Med* 2005; **10**: 185–94.

4 Baughman RP. The use of carbapenems in the treatment of serious infections. *J Intensive Care Med* 2009; **24**: 230–41.

5 Rodloff AC, Goldstein EJ, Torres A. Two decades of imipenem therapy. *J Antimicrob Chemother* 2006; **58**: 916–29.

6 Freij BJ, McCracken GH Jr, Olsen KD *et al.* Pharmacokinetics of imipenem-cilastatin in neonates. *Antimicrob Agents Chemother* 1985; **27**: 431–5.

7 Gruber WC, Rench MA, Garcia-Prats JA *et al.* Single-dose pharmacokinetics of imipenem-cilastatin in neonates. *Antimicrob Agents Chemother* 1985; **27**: 511–4.

8 Reed MD, Kliegman RM, Yamashita TS *et al.* Clinical pharmacology of imipenem and cilastatin in premature infants during the first week of life. *Antimicrob Agents Chemother* 1990; **34**: 1172–7.

9 Böswald M, Döbig C, Kändler C *et al.* Pharmacokinetic and clinical evaluation of serious infections in premature and newborn infants under therapy with imipenem/cilastatin. *Infection* 1999; **27**: 299–304.

10 Begue PC, Baron S, Challier P *et al.* Pharmacokinetic and clinical evaluation of imipenem/cilastatin in children and neonates. *Scand J Infect Dis Suppl* 1987; **52**: 40–5.

11 Yoshizawa K, Ikawa K, Ikeda K *et al.* Population pharmacokinetic-pharmacodynamic target attainment analysis of imipenem plasma and urine data in neonates and children. *Pediatr Infect Dis J* 2013; **32**: 1208–16.

12 Pacifici GM, Allegaert K. Clinical pharmacology of carbapenems in neonates. *J Chemother* 2014; **26**: 67–73.

13 Kearns GL, Abdel-Rahman SM, Alander SW *et al.* Developmental pharmacology–drug disposition, action, and therapy in infants and children. *N Engl J Med* 2003; **349**: 1157–67.

14 *Product Information: PRIMAXIN(R) Intravenous Injection, Imipenem Cilastatin Intravenous Injection.* Whitehouse Station, NJ: Merck Sharp & Dohme Corp (per FDA), 2016.

15 Bradley JS, Sauberan JB, Ambrose PG *et al.* Meropenem pharmacokinetics, pharmacodynamics, and Monte Carlo simulation in the neonate. *Pediatr Infect Dis J* 2008; **27**: 794–9.

16 Giannoni E, Moreillon P, Cotting J *et al.* Prospective determination of plasma imipenem concentrations in critically ill children. *Antimicrob Agents Chemother* 2006; **50**: 2563–8.

17 Wahlby U, Thomson AH, Milligan PA *et al.* Models for time-varying covariates in population pharmacokinetic-pharmacodynamic analysis. *Br J Clin Pharmacol* 2004; **58**: 367–77.

18 Bioanalytical Method Validation Guidance for Industry by the FDA. 2020. https://www.fda.gov/files/drugs/published/Bioanalytical-Method-Validation-Guidance-for-Industry.pdf.

19 Decosterd LA, Mercier T, Ternon B *et al.* Validation and clinical application of a multiplex high performance liquid chromatography - tandem mass spectrometry assay for the monitoring of plasma concentrations of 12 antibiotics in patients with severe bacterial infections. *J Chromatogr B Analyt Technol Biomed Life Sci* 2020; **1157**: 122160.

20 van den Anker JN, Schwab M, Kearns GL. Developmental pharmacokinetics. *Handb Exp Pharmacol* 2011; **205**: 51–75.

21 Holford N, Heo YA, Anderson B. A pharmacokinetic standard for babies and adults. *J Pharm Sci* 2013; **102**: 2941–52.

22 Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. *Annu Rev Pharmacol Toxicol* 2008; **48**: 303–32.

23 Tod M, Lokiec F, Bidault R *et al.* Pharmacokinetics of oral acyclovir in neonates and in infants: a population analysis. *Antimicrob Agents Chemother* 2001; **45**: 150–7.

24 Anderson BJ, Allegaert K, Holford NH. Population clinical pharmacology of children: modelling covariate effects. *Eur J Pediatr* 2006; **165**: 819–29.

25 Ahn JE, Karlsson MO, Dunne A *et al.* Likelihood based approaches to handling data below the quantification limit using NONMEM VI. *J Pharmacokinet Pharmacodyn* 2008; **35**: 401–21.

26 van den Anker JN, de Groot R, Broerse HM *et al.* Assessment of glomerular filtration rate in preterm infants by serum creatinine: comparison with inulin clearance. *Pediatrics* 1995; **96**: 1156–8.

27 van Donge T, Allegaert K, Gotta V *et al.* Characterizing dynamics of serum creatinine and creatinine clearance in extremely low birth weight neonates during the first 6 weeks of life. *Pediatr Nephrol* 2021; **36**: 649–59.

28 Lindbom L, Pihlgren P, Jonsson EN. PsN-Toolkit–a collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. *Comput Methods Programs Biomed* 2005; **79**: 241–57.

29 Bergstrand M, Hooker AC, Wallin JE *et al.* Prediction-corrected visual predictive checks for diagnosing nonlinear mixed-effects models. *AAPS J* 2011; **13**: 143–51.

30 Jonsson EN, Karlsson MO. Xpose–an S-PLUS based population pharmacokinetic/pharmacodynamic model building aid for NONMEM. *Comput Methods Programs Biomed* 1999; **58**: 51–64.

31 Drusano GL. Antimicrobial pharmacodynamics: critical interactions of 'bug and drug'. *Nat Rev Microbiol* 2004; **2**: 289–300.

32 Roberts JA, Paul SK, Akova M *et al.* DALI: defining antibiotic levels in intensive care unit patients: are current β-lactam antibiotic doses sufficient for critically ill patients? *Clin Infect Dis* 2014; **58**: 1072–83.

33 Abdul-Aziz MH, Lipman J, Roberts JA. Identifying "at-risk" patients for sub-optimal β-lactam exposure in critically ill patients with severe infections. *Crit Care* 2017; **21**: 283.

34 Burger R, Guidi M, Calpini V *et al.* Effect of renal clearance and continuous renal replacement therapy on appropriateness of recommended meropenem dosing regimens in critically ill patients with susceptible life-threatening infections. *J Antimicrob Chemother* 2018; **73**: 3413–22.

35 European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 11.0. 2021. https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_11.0_Breakpoint_Tables.pdf.

36 Duffull SB, Wright DF, Winter HR. Interpreting population pharmacokinetic-pharmacodynamic analyses - a clinical viewpoint. *Br J Clin Pharmacol* 2011; **71**: 807–14.

37 Holford N. Dosing in children. *Clin Pharmacol Ther* 2010; **87**: 367–70.

38 Dao K, Guidi M, André P *et al.* Optimisation of vancomycin exposure in neonates based on the best level of evidence. *Pharmacol Res* 2019; **154**: 104278.

39 Anderson BJ, Holford NH. Tips and traps analyzing pediatric PK data. *Paediatr Anaesth* 2011; **21**: 222–37.

40 Abitbol CL, Seeherunvong W, Galarza MG *et al.* Neonatal kidney size and function in preterm infants: what is a true estimate of glomerular filtration rate? *J Pediatr* 2014; **164**: 1026–31. e2.

41 Schwartz GJ, Munoz A, Schneider MF *et al.* New equations to estimate GFR in children with CKD. *J Am Soc Nephrol* 2009; **20**: 629–37.

42 De Paepe P, Belpaire FM, Buylaert WA. Pharmacokinetic and pharmacodynamic considerations when treating patients with sepsis and septic shock. *Clin Pharmacokinet* 2002; **41**: 1135–51.

43 Yoshizawa K, Ikawa K, Ikeda K *et al.* 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**: 427–33.

44 Novelli A, Adembri C, Livi P *et al.* Pharmacokinetic evaluation of meropenem and imipenem in critically ill patients with sepsis. *Clin Pharmacokinet* 2005; **44**: 539–49.

45 Dreetz M, Hamacher J, Eller J *et al.* Serum bactericidal activities and comparative pharmacokinetics of meropenem and imipenem-cilastatin. *Antimicrob Agents Chemother* 1996; **40**: 105–9.

46 Boucher BA, Hickerson WL, Kuhl DA *et al.* Imipenem pharmacokinetics in patients with burns. *Clin Pharmacol Ther* 1990; **48**: 130–7.

47 Drusano GL, Standiford HC, Bustamante C *et al.* Multiple-dose pharmacokinetics of imipenem-cilastatin. *Antimicrob Agents Chemother* 1984; **26**: 715–21.

48 Jacobs RF, Kearns GL, Trang JM *et al.* Single-dose pharmacokinetics of imipenem in children. *J Pediatr* 1984; **105**: 996–1001.

49 Couffignal C, Pajot O, Laouénan C *et al.* Population pharmacokinetics of imipenem in critically ill patients with suspected ventilator-associated pneumonia and evaluation of dosage regimens. *Br J Clin Pharmacol* 2014; **78**: 1022–34.

50 Ikawa K, Morikawa N, Sakamoto K *et al.* Pharmacokinetics and pharmacodynamic assessment of imipenem in the intraperitoneal fluid of abdominal surgery patients. *Chemotherapy* 2008; **54**: 131–9.

51 Dailly E, Kergueris MF, Pannier M *et al.* Population pharmacokinetics of imipenem in burn patients. *Fundam Clin Pharmacol* 2003; **17**: 645–50.

52 Tegeder I, Bremer F, Oelkers R *et al.* Pharmacokinetics of imipenem-cilastatin in critically ill patients undergoing continuous venovenous hemofiltration. *Antimicrob Agents Chemother* 1997; **41**: 2640–5.

53 Ariano RE, Nyhlén A, Donnelly JP *et al.* Pharmacokinetics and pharmacodynamics of meropenem in febrile neutropenic patients with bacteremia. *Ann Pharmacother* 2005; **39**: 32–8.

54 Shabaan AE, Nour I, Elsayed Eldegla H *et al.* Conventional versus prolonged infusion of meropenem in neonates with gram-negative late-onset sepsis: a randomized controlled trial. *Pediatr Infect Dis J* 2017; **36**: 358–63.

55 Calandra G, Lydick E, Carrigan J *et al.* Factors predisposing to seizures in seriously ill infected patients receiving antibiotics: experience with imipenem/cilastatin. *Am J Med* 1988; **84**: 911–8.

56 Alvan G, Nord CE. Adverse effects of monobactams and carbapenems. *Drug Saf* 1995; **12**: 305–13.

57 Lamoth F, Erard V, Asner S *et al.* High imipenem blood concentrations associated with toxic encephalopathy in a patient with mild renal dysfunction. *Int J Antimicrob Agents* 2009; **34**: 386–8.

58 Dubovitskaya AB, Schumacher M, Aberer K, Thoma Y. TUCUXI: an intelligent system for personalized medicine from individualization of treatments to research databases and back. In: *Proceedings of the 8th ACM International Conference on Bioinformatics, Computational Biology, and Health Informatics,* Boston, USA, 2017: 223–32.

59 Ainsworth SB. Imipenem with cilastatin. In: *Neonatal Formulary: Drug Use in Pregnancy and the First Year of Life,* 7th edn. John Wiley & Sons, 2015: 264–265.

60 Paediatric Formulary Committee. *BNF for Children (BNFC) 2016–2017.* Pharmaceutical Press, 2016: 295–6.

61 *Micromedex Neofax Essentials®, A Manual of Drugs Used in Neonatal Care.* Thomson Reuters, 2014: 426.

62 American Academy of Pediatrics. Tables of antibacterial drug dosages. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red Book: 2012 Report of the Committee on Infectious Diseases.* American Academy of Pediatrics, 2012: 807–20.