J Antimicrob Chemother 2013; **68**: 2600–2608
doi:10.1093/jac/dkt240 Advance Access publication 25 June 2013

Journal of Antimicrobial Chemotherapy

Population pharmacokinetics and dosing simulations of amoxicillin/clavulanic acid in critically ill patients

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Received 8 April 2013; returned 1 May 2013; revised 15 May 2013; accepted 19 May 2013

Objectives: The objective of this study was to investigate the population pharmacokinetics and pharmacodynamics of amoxicillin and clavulanic acid in critically ill patients.

Methods: In this observational pharmacokinetic study, multiple blood samples were taken over one dosing interval of intravenous amoxicillin/clavulanic acid (1000/200 mg). Blood samples were analysed using a validated ultra HPLC–tandem mass spectrometry technique. Population pharmacokinetic analysis and dosing simulations were performed using non-linear mixed-effects modelling.

Results: One-hundred-and-four blood samples were collected from 13 patients. For both amoxicillin and clavulanic acid, a two-compartment model with between-subject variability for both the clearance and the volume of distribution of the central compartment described the data adequately. For both compounds, 24 h urinary creatinine clearance was supported as a descriptor of drug clearance. The mean clearance of amoxicillin was 10.0 L/h and the mean volume of distribution was 27.4 L. For clavulanic acid, the mean clearance was 6.8 L/h and the mean volume of distribution was 19.2 L. Dosing simulations for amoxicillin supported the use of standard dosing regimens (30 min infusion of 1 g four-times daily or 2 g three-times daily) for most patients when using a target MIC of 8 mg/L and a pharmacodynamic target of 50% $fT_{>MIC}$, except for those with a creatinine clearance >190 mL/min. Dosing simulations for clavulanic acid showed little accumulation when high doses were administered to patients with high creatinine clearance.

Conclusions: Although vast pharmacokinetic variability exists for both amoxicillin and clavulanic acid in intensive care unit patients, current dosing regiments are appropriate for most patients, except those with very high creatinine clearance.

Keywords: β-lactams, amoxicillin, antibiotics, PK/PD, critical care medicine, ICU, clavulanic acid

Introduction

Infection is an important problem in critical care medicine. In a recent point prevalence study, 71% of >13 000 patients admitted to intensive care units (ICUs) around the world received antibiotic therapy.[1] Sepsis alone is the leading cause of mortality in non-cardiac ICUs, with up to 30% of patients dying within 1 month of diagnosis.[2] Currently, timely and appropriate antibiotic therapy after source control is considered to be the mainstay of treatment.[3] However, it is important that adequate concentrations are achieved.[4]

Amoxicillin is a semi-synthetic penicillin that has been in clinical use for decades. It is commonly administered with the β-lactamase inhibitor clavulanic acid to broaden its antibacterial spectrum of activity. In ICUs, amoxicillin/clavulanic acid is used for community-acquired infections caused by both Gram-positive and Gram-negative organisms inclusive of anaerobes.[5] Specific indications include community-acquired pneumonia, intra-abdominal infections and skin and soft tissue infections.

β-Lactam antibiotics exhibit a time-dependent killing pattern, meaning that the percentage time above the MIC ($fT_{>MIC}$) for the microorganism is considered the best determinant of the efficacy of these antibiotics. For penicillins, 50% $fT_{>MIC}$ is considered the minimum pharmacodynamic target for maximal bacterial killing.[6] However, research in critically ill patients shows that higher pharmacokinetic/pharmacodynamic targets, such as

100% $fT_{>MIC}$ or even 100% $fT_{>4\times MIC}$, may be associated with better outcomes.[7,8]

Numerous studies have already investigated the population pharmacokinetics of broad-spectrum antibiotics in critically ill patients,[9–17] all of which highlight the different pharmacokinetics of these drugs in comparison with healthy volunteers and highlight the need for individual dosing of these antibiotics in critically ill patients. However, if research is only focused on these broad-spectrum antibiotics, this may encourage physicians to favour using these antibiotics, even when more targeted therapies could be just as effective, only because these broad-spectrum antibiotics have been investigated in this special patient population. This is why data on more targeted therapies are equally relevant.[18]

Although amoxicillin/clavulanic acid is commonly used in critically ill patients, there are few data to guide the dosing of amoxicillin and clavulanic acid in this specific patient population. Therefore, the aim of this study was to evaluate the population pharmacokinetics of amoxicillin and clavulanic acid in ICU patients and investigate if pharmacokinetic/pharmacodynamic targets are achieved with current dosing strategies, as well as to investigate the potential of alternative dosing regimens and strategies.

Methods

Patients

This prospective, open-label pharmacokinetic study was conducted in the ICU of Ghent University Hospital, Belgium, between March and July 2012. The trial was conducted in accordance with the Declaration of Helsinki. The study was approved by the Ethics Committee of Ghent University Hospital (registration number 2012/078) and was registered with the European Union Drug Regulating Authorities Clinical Trials (EudraCT, registration number 2011-006107-35). Written informed consent was obtained from all patients or a legally authorized representative before enrolment. Patients were enrolled in the study if they were admitted to the ICU and were prescribed amoxicillin/clavulanic acid. The exclusion criteria included <18 years of age, a haematocrit of <21%, absence of an arterial catheter or a need for renal replacement therapy.

Drug administration

Amoxicillin/clavulanic acid (Augmentin®, GlaxoSmithKline, Genval, Belgium) was infused intravenously over 30 min using a syringe pump. Amoxicillin/clavulanic acid (1000/200 mg) was dosed four-times daily for patients with normal renal function and three-times daily for patients with renal impairment, defined as a 24 h urinary creatinine clearance of <30 mL/min.

Study procedures

Blood samples for assay were obtained at assumed pharmacokinetic steady-state (≥24 h of therapy) through a separate arterial catheter. Blood samples were collected just before the start of infusion (time 0) and after 0.25, 0.5, 0.75, 1, 2, 4, 6 or 8 h (depending on dose interval) in lithium-heparinized collection tubes (Venosafe, Terumo, Leuven, Belgium). The blood samples were centrifuged for 10 min at 3000 **g** (ALC Centrifugette 4206, Analis, Gent, Belgium) immediately after sample collection and then frozen on dry ice and finally stored at −80°C (within 1 h after sample collection) for a maximum of 4 weeks until assay.

In order to determine the 24 h creatinine clearance, the patient's urine was collected, starting at the time of initiation of the antibiotic infusion. The plasma sample at time 0 was also used to determine the concentration of creatinine in the blood. Additional data were obtained from the medical records and included participant demographics, clinical details, measures of illness severity, microbiological results and laboratory investigations.

Analytical methods

The plasma samples were analysed in the toxicology laboratory of the Department of Laboratory Medicine, Ghent University Hospital. The plasma concentrations of amoxicillin and clavulanic acid were determined by validated ultra HPLC (UPLC) coupled to tandem mass spectrometry. The details of this method have been previously described elsewhere.[19] In brief, sample preparation included protein precipitation with acetonitrile and back-extraction of acetonitrile with dichloromethane. Amoxicillin-d_4 was used as an internal standard. Chromatographic separation was performed on a Waters Acquity UPLC system using a BEH C_{18} column (1.7 μm, 100×2.1 mm), applying a binary gradient elution of water and acetonitrile both containing 0.1% formic acid. The total runtime was 5.5 min. The lower limit of quantification was 0.5 mg/L and the imprecision was <15% at all levels. Observed concentrations for amoxicillin were corrected for protein binding (17%).[5]

Creatinine was measured in both plasma and urine using the rate blanked, compensated and uncompensated Jaffe technique, respectively (Modular P and Cobas 6000, Roche Diagnostics GmbH, Mannheim, Germany). The creatinine clearance was calculated as follows:

24 h creatinine clearance $= V_u \times U_{cr}/(1440 \times S_{cr})$, where V_u is the urinary volume (mL), U_{cr} the urinary creatinine concentration (μmol/L) and S_{cr} the serum creatinine concentration (μmol/L).

Pharmacokinetic analysis

The concentration–time data were analysed using non-linear mixed-effects modelling (NONMEM version 6.1, Globomax LLC, Hanover, MD, USA). A Digital Fortran compiler was used and the runs were executed using Wings for NONMEM (http://wfn.sourceforge.net). The first-order conditional estimation method with interaction was used throughout the model building.

For the population pharmacokinetic analysis, the plasma amoxicillin concentrations were fitted to one-, two- or three-compartment linear models using subroutines from the NONMEM library.

Between-subject variability (BSV)

BSV was evaluated using an exponential variability model. Various models for residual unexplained variability were also tested.

Model diagnostics

Visual inspection of the diagnostic scatter plots and the NONMEM objective function value (OFV) were used to evaluate the goodness of fit. Statistical comparison of nested models was undertaken in the NONMEM program using log-likelihood ratios, which are assumed to be χ^2 distributed. On the basis of a χ^2 test of the difference in OFV, a decrease in the OFV of 3.84 U ($P<0.05$) for one degree of freedom was considered statistically significant. Decreases in BSV of one of the parameters of ≥10% were also accepted for inclusion of a more complicated model.

Covariate screening

Covariate model building was performed in a stepwise fashion with forward inclusion and backward deletion based upon the aforementioned model selection criteria. Creatinine clearance, age, sex, weight, Acute Physiology and Chronic Health Evaluation (APACHE) II score and Sequential Organ Failure Assessment (SOFA) score were evaluated as covariates.

Bootstrap

A non-parametric bootstrap method ($n=1000$) was used to study the uncertainty of the pharmacokinetic parameter estimates in the final model. From the bootstrap empirical posterior distribution, we were able to obtain the 95% CI (2.5%–97.5% percentile) for the parameters, as described previously.[20]

Dosing simulations

As creatinine clearance was the only covariate retained in the final model, only the effects of different creatinine clearances were simulated. The creatinine clearances simulated were 10, 30, 50, 100, 130, 150 and 190 mL/min. The simulated dosages for amoxicillin are summarized in Table 1.

The ability of each dosing regimen to achieve predefined pharmacodynamic targets (50% $fT_{>MIC}$) was then assessed. The target MIC was the highest MIC for which the antibiotic is used according to EUCAST breakpoints, which is 8 mg/L, the EUCAST breakpoint for *Enterobacter* spp., *Klebsiella* spp., *Citrobacter* spp. and *Escherichia coli*.

Performing dosing simulations for clavulanic acid to evaluate efficacy was not undertaken as the pharmacodynamic target is not clear. Therefore, simulations for clavulanic acid could only be undertaken to investigate whether accumulation of clavulanic acid occurs if the dose or frequency of amoxicillin/clavulanic acid administration is increased. Dosing simulations were performed for creatinine clearances of 30, 50, 130 and 190 mL/min for both a low and high dose of amoxicillin/clavulanic acid (Table 2).

Validation of the model

The model for amoxicillin was validated using data from 14 independent patients enrolled as part of another pharmacokinetic study.[21] Two concentrations were available per patient. Validation was performed by comparing the observed versus predicted concentrations using a coefficient of determination (R^2).

Results

Patient characteristics

A total of 104 blood samples and 13 creatinine clearances were analysed from 13 patients enrolled in this study. The demographic and general clinical characteristics are shown in Table 3. The most frequent reason for the antibiotic therapy was a pulmonary infection.

Table 1. Simulated dosages for amoxicillin

Intermittent	Extended	Continuous
No loading dose	no loading dose	loading dose: 1 g over 0.5 h
Infusion time 0.5 h	infusion time = half of dosing interval	constant infusion over 24 h
0.5 g q4h	0.5 g q4h	
0.5 g q6h	0.5 g q6h	
0.5 g q8h	0.5 g q8h	
1 g q4h	1 g q4h	6 g q24h
1 g q6h	1 g q6h	4 g q24h
1 g q8h	1 g q8h	3 g q24h
2 g q6h	2 g q6h	8 g q24h
2 g q8h	2 g q8h	
	3 g q6h	12 g q24h

q4h, six-times daily; q6h, four-times daily; q8h, three-times daily; q24h, dose administered over 24 h.

Table 2. Tested doses for dosing simulations to determine potential accumulation of clavulanic acid

CL_{CR} (mL/min)	High-dose amoxicillin/clavulanic acid (mg)	Low-dose amoxicillin/clavulanic acid (mg)
30	2000/400 q8h	500/100 q8h
50	2000/400 q6h	500/100 q6h
130	2000/400 q4h	500/100 q4h
190	2000/400 q4h	500/100 q4h

CL_{CR}, creatinine clearance; q8h, three-times daily; q6h, four-times daily; q4h, six-times daily.

Table 3. Patient characteristics

Patient characteristic	Value
Age (years), median (IQR)	62 (58–72)
Weight (kg), median (IQR)	75 (70–79)
BMI, median (IQR)	24 (21–25)
Male, %	85
APACHE II score on ICU admission, median (IQR)	25 (18–29)
SOFA score on ICU admission, median (IQR)	9 (5–12)
SOFA score following dose administration, median (IQR)	6 (4–12)
Creatinine clearance (mL/min), median (IQR)	102 (50–157)

BMI, body mass index.

Pharmacokinetic analysis

For both compounds, the best base model consisted of a two-compartment linear model with zero-order input with exponential residual unknown variability for amoxicillin and combined additive–exponential residual unknown variability for clavulanic acid. BSV was included for both clearance and for volume of distribution of the central compartment for both compounds.

The typical value of clearance was calculated as a function of creatinine clearance, normalized to the population's median creatinine clearance, 102 mL/min (equation 1 for amoxicillin and equation 2 for clavulanic acid), where θ_{1a} is the typical value of amoxicillin clearance ($TVCL_a$) in the population and θ_{1c} is the typical value of clavulanic acid clearance ($TVCL_c$) in the population.

$$TVCL_a = \theta_{1a} \times \left(\frac{CL_{CR}}{102}\right) \quad (1)$$

$$TVCL_c = \theta_{1c} \times \left(\frac{CL_{CR}}{102}\right) \quad (2)$$

The addition of creatinine clearance as a covariate greatly improved the model fit for both compounds. None of the other covariates statistically significantly improved the model and, therefore, they could not be included.

Figure 1 displays the goodness-of-fit plots for the final model for both compounds. Of the 104 samples included in the analysis, only

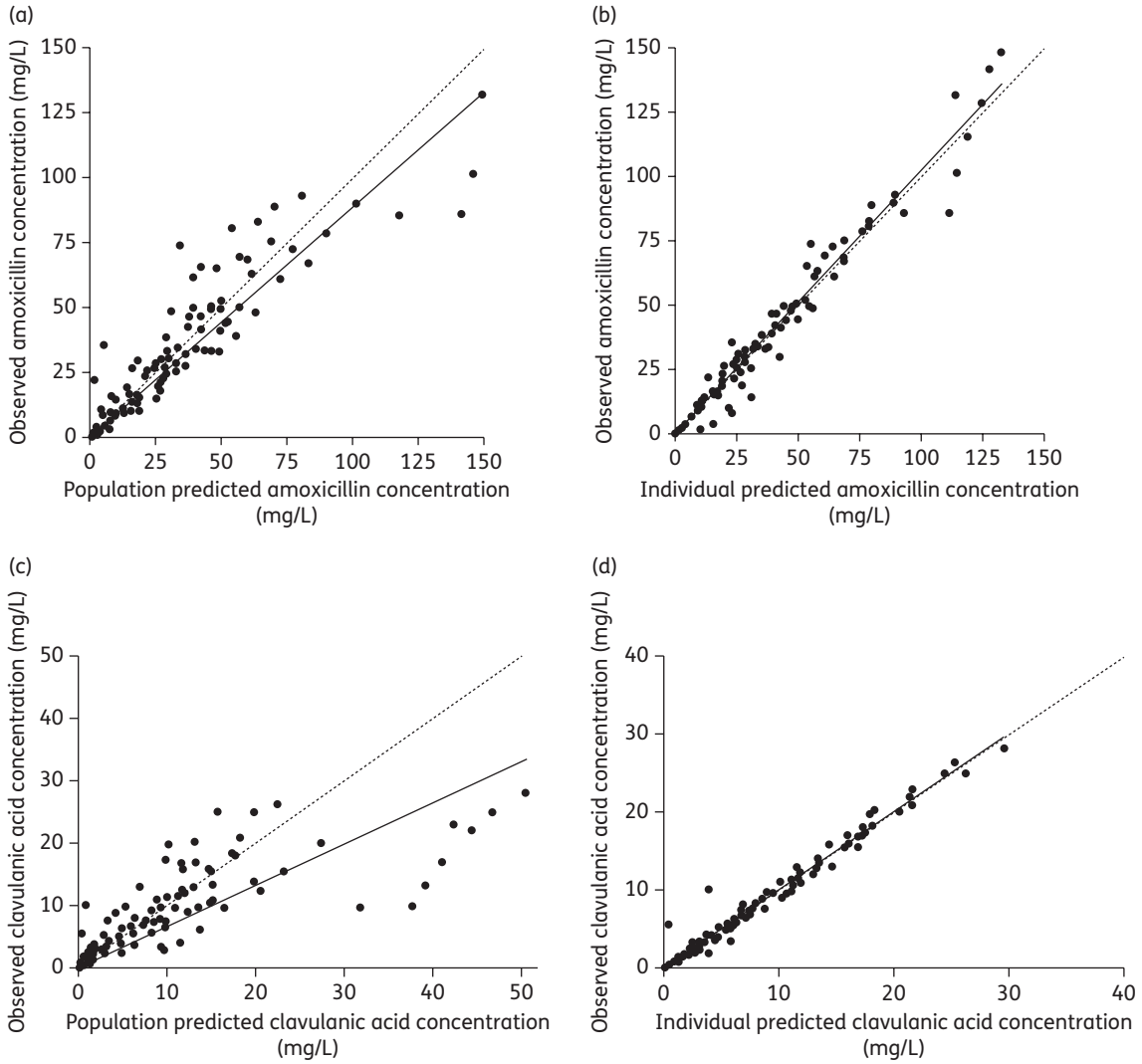

Figure 1. Diagnostic plots for the final population pharmacokinetic covariate model. (a) Population predicted amoxicillin concentrations versus observed amoxicillin concentrations ($R^2=0.87$). (b) Individual predicted amoxicillin concentrations versus observed amoxicillin concentrations ($R^2=0.96$). (c) Population predicted clavulanic acid concentrations versus observed clavulanic acid concentrations ($R^2=0.44$). (d) Individual predicted clavulanic acid concentrations versus observed clavulanic acid concentrations ($R^2=0.98$). The non-linear regression line of fit is shown by the continuous line and the line of *xy* is the broken line.

5 samples had a concentration greater than two standard deviations outside that predicted by the model for amoxicillin and only 2 samples had a concentration greater than two standard deviations outside that predicted by the model for clavulanic acid, which we considered acceptable given the level of sickness severity and likely pharmacokinetic heterogeneity of the patient cohort. All other visual predictive checks were acceptable and confirmed the goodness of fit of the model. The plots in Figure 1 show that the final pharmacokinetic model describes the measured concentrations adequately. All subsequent dosing simulations were then based on this model.

The values of the parameters for the final models are given in Table 4 and include the 95% CIs for the parameters computed from all bootstrap runs.

Dosing simulations

The results of the dosing simulations for amoxicillin are summarized in Table 5, which shows whether the target of 50% or 100% $fT_{>MIC}$ will be achieved for different values of creatinine clearance and different dosing strategies.

The standard dose of 1 g of amoxicillin four-times daily or 2 g of amoxicillin three-times daily results in adequate exposure for both low and normal creatinine clearances. However, dependent on the chosen target, standard dosing will not suffice for patients with high creatinine clearance infected with a microorganism with a high MIC_{90} (8 mg/L). Patients with a creatinine clearance of 190 mL/min do not even achieve 50% $fT_{>MIC}$, which is considered the minimal pharmacokinetic target needed for bacterial killing, if standard dosing regimens are used.

Table 4. Bootstrap parameter estimates of the final covariate model

	Amoxicillin				Clavulanic acid			
		bootstrap				Bootstrap		
			95% CI				95% CI	
Parameter	model mean	mean	2.5%	97.5%	model mean	mean	2.5%	97.5%
Fixed effects								
CL (L/h)	10.0	10.3	8.6	12.6	6.8	9.4	6.3	12.9
V_c (L)	13.7	13.5	10.2	17.7	7.6	8.1	6.8	9.9
V_p (L)	13.7	14.1	11.7	27.7	11.6	14.7	8.4	63.1
Q (L/h)	15.6	15.7	12.2	19.6	10.4	10.0	8.6	11.5
Random-effects BSV (% CV)								
CL (L/h)		39.9	25.3	53.6		57.8	31.1	85.5
V_c (L)		38.7	4.0	67.1		34.7	22.8	44.8
Random error								
RUV (% CV)		22.0	10.1	32.9				
RUV (SD, mg/L)						1.2	0.7	1.7

CL, clearance; V_c, volume of distribution of the central compartment; V_p, volume of distribution of the peripheral compartment; Q, intercompartmental clearance; RUV, residual unexplained variability; CV, coefficient of variation; SD, standard deviation.

The results of the dosing simulations for amoxicillin and clavulanic acid are shown in Figure 2(a–d), which shows the concentrations of amoxicillin and clavulanic acid over a 7 day course for both a low and a high dose for different values of creatinine clearance. These figures show that little accumulation of clavulanic acid occurs if higher doses of amoxicillin/clavulanic acid are administered to patients with normal to high creatinine clearance.

Validation

Similar to the characteristics of the patients used to build the model, the main indication for antibiotic therapy was also treatment of a pulmonary infection. The median creatinine clearance was 97.5 (IQR 44–125) mL/min, which was comparable to the creatinine clearance of the patients in the present study, for whom the median creatinine clearance was 102 (IQR 50–157) mL/min ($P=0.685$).

The results of the external validation are shown graphically in Figure 3. The coefficient of determination was 0.75 and was found to be statistically significant ($P<0.0001$).

Discussion

Although amoxicillin/clavulanic acid is frequently used to treat severe infections in critically ill patients, this is the first known paper to investigate its population pharmacokinetics in ICU patients. We found that both amoxicillin and clavulanic acid clearance were proportional to creatinine clearance, with important variability between patients for antibiotic clearance. Current dosing schemes are adequate for patients without increased creatinine clearances when minimal pharmacokinetic/pharmacodynamic targets are used.

Clearance appears to be an important factor in the variability described. This pharmacokinetic variability is typical for ICU patients and has been shown for other β-lactams as well. The available pharmacokinetic studies in healthy volunteers show a mean clearance of ∼12.5 L/h for amoxicillin, with a coefficient of variation of ∼20%.[22–24] This is in contrast to our findings of a mean clearance of 10.0 L/h with a coefficient of variation of >80% in the 13 patients included in this study, which highlights the importance of studying this specific patient population. The values observed for the volume of distribution (IQR 24.7–30.7 L) seem to be comparable to those found in literature for healthy volunteers.[22–24] As there are no population pharmacokinetic studies published for clavulanic acid, it was not possible to compare our results to the results previously described in the literature.

The EUCAST breakpoint MIC of amoxicillin for common respiratory pathogens, such as *Staphylococcus aureus* (2 mg/L) and *Streptococcus pneumoniae* (0.064 mg/L), is low. However, this is far higher for other species, such as *Enterobacter* spp., *E. coli* and *Klebsiella* spp., for which it is 8 mg/L, which is a potential consideration with community-acquired intra-abdominal infection.[25] By performing dosing simulations for amoxicillin and investigating the probability of target attainment, we have demonstrated that intermittent infusion of amoxicillin at 1 g four-times daily or 2 g three-times daily will ensure plasma free concentrations exceeding this breakpoint MIC for ≥50% $fT_{>MIC}$—which is considered the minimum pharmacokinetic/pharmacodynamic target to achieve bacterial killing—for patients with low and normal kidney function. However, using the same dosing strategy, patients with very high creatinine clearances (190 mL/min) will not reach this target. In order to achieve sufficient exposure, these patients need more frequent antibiotic administration (1 g six-times daily) or need to be treated with alternate dosing strategies. This means that standard dosing should lead to sufficient pharmacokinetic/pharmacodynamic

Table 5. Effect of creatinine clearances and different dosing strategies on the probability of target attainment for amoxicillin (50% $fT_{>MIC}$ and 100% $fT_{>MIC}$)

	MIC					
	<4 mg/L		8 mg/L		16 mg/L	
Dose	50% $fT_{>MIC}$	100% $fT_{>MIC}$	50% $fT_{>MIC}$	100% $fT_{>MIC}$	50% $fT_{>MIC}$	100% $fT_{>MIC}$
Creatinine clearance 30 mL/min						
II 0.5 g q6h						
II 0.5 g q8h	+	+	+	+	+	−
II 1 g q8h	+	+	+	+	+	+
II 1 g q6h	+	+	+	+	+	+
Creatinine clearance 50 mL/min						
II 0.5 g q6h	+	+	+	+	+	−
II 1 g q8h	+	+	+	+	+	−
EI 1 g q8h	+	+	+	+	+	+
II 1 g q6h	+	+	+	+	+	+
CI 4 g q24h	+	+	+	+	+	+
Creatinine clearance 130 mL/min						
II 1 g q8h	+	−	−	−	−	−
II 1 g q6h	+	+	+	−	−	−
EI 1 g q6h	+	+	+	−	+	−
CI 4 g q24h	+	+	+	+	−	−
II 1 g q4h	+	+	+	+	+	−
CI 6 g q24h	+	+	+	+	+	+
Creatinine clearance 190 mL/min						
II 1 g q6h	+	−	−	−	−	−
EI 1 g q6h	+	+	+	−	−	−
CI 4 g q24h	+	+	+	−	−	−
II 1 g q4h	+	+	+	−	−	−
CI 6 g q24h	+	+	+	+	+	−
EI 2 g q6h	+	+	+	−	+	−
CI 8 g q24h	+	+	+	+	+	+
EI 3 g q6h	+	+	+	+	+	−

q4h, six-times daily; q6h, four-times daily; q8h, three-times daily; q24h, dose administered over 24 h; II, intermittent infusion; EI, extended infusion; CI, continuous infusion; +, target attained; −, target not attained.

exposure when treating an infection caused by an organism with a low MIC (in the case of a respiratory tract infection), but may fail to achieve sufficient pharmacokinetic/pharmacodynamic exposure when treating an infection caused by an organism with a high MIC (in the case of an intra-abdominal infection), when the creatinine clearance is >190 mL/min. Moreover, it is important to state that estimations of glomerular filtration rate (GFR), such as the Cockcroft–Gault and Modified Diet in Renal Disease equations, are not reliable in ICU patients, and are surely not reliable to assess augmented renal clearance, as this is reported as >60 or >90 mL/min. In these patients, 8 or 24 h urinary creatinine clearance should be preferred.[26–28]

Moreover, research in critically ill patients shows that higher pharmacokinetic/pharmacodynamic targets may be associated with better outcomes.[7,8] If one aims to achieve these higher targets, such as 100% $fT_{>MIC}$ or even 100% $fT_{>4\times MIC}$, more frequent dosing or administration by prolonged infusion is necessary for patients with normal to high renal function. Amoxicillin is stable for up to 24 h for a concentration range of 20–40 g/L.[29] However, the stability of clavulanic acid when used as a prolonged infusion is unknown. In addition, more frequent dosing or alternate dosing strategies could also be a way to treat more resistant microorganisms, which would otherwise be classified as not sensitive to this antibiotic, which may be very valuable in this era of increasing resistance. The advantage of using extended or continuous infusion on pharmacokinetic/pharmacodynamic target attainment has already been shown for other β-lactams as well.[30–32]

As for clavulanic acid, dosing simulations were only performed to evaluate accumulation, since the pharmacodynamic target for efficacy is unknown. We have shown that there is little accumulation of clavulanic acid in patients with high creatinine clearance treated for 7 days with a high dose of amoxicillin/clavulanic acid.

This paper has a number of limitations. First, we did not investigate free concentrations or concentrations at the site of infection. Instead, we measured total drug concentrations with correction for protein binding based on the literature. This is an

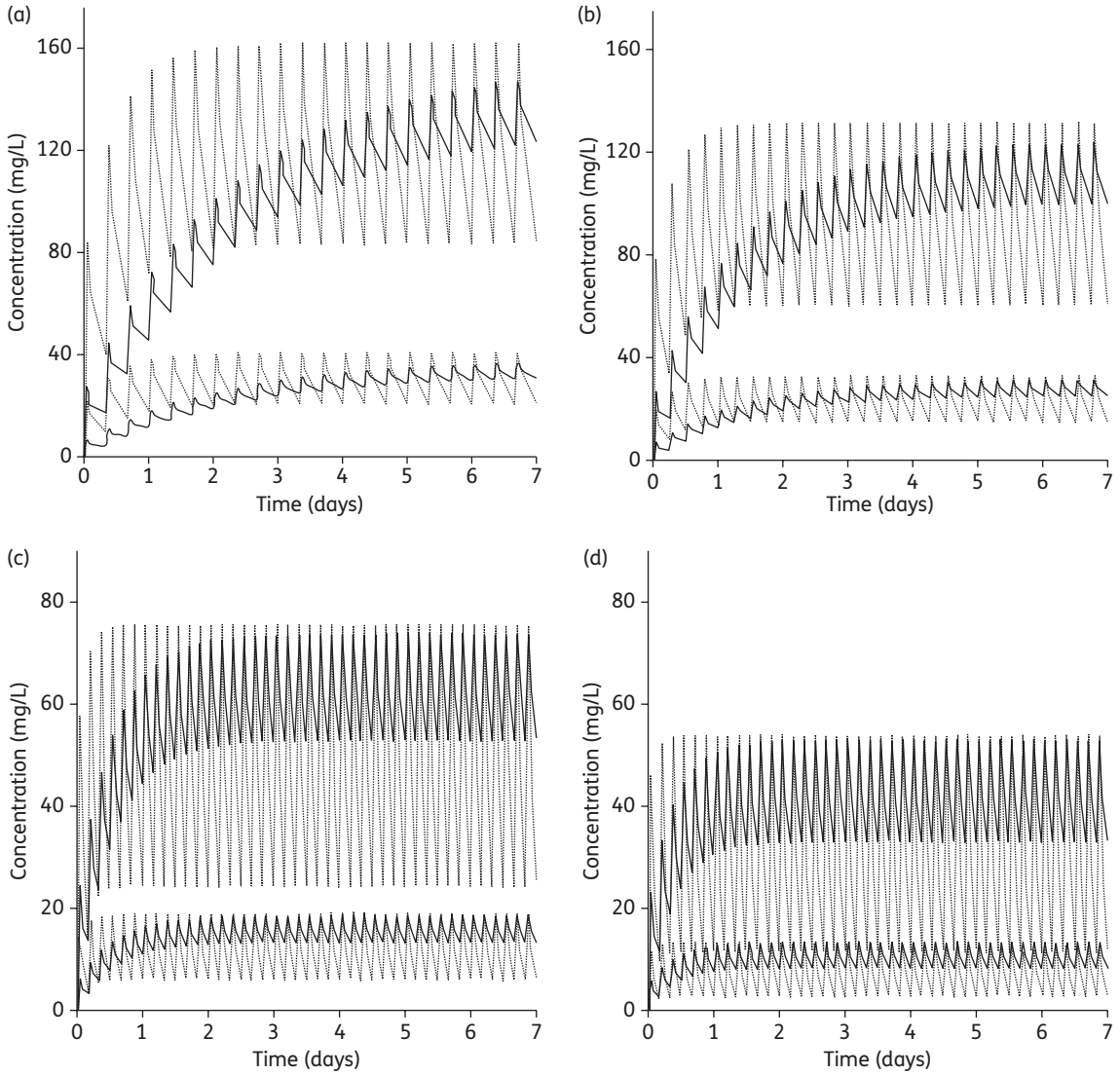

Figure 2. Dosing simulations for amoxicillin and clavulanic acid in high and low dose for different creatinine clearances. (a) Concentration versus time for a patient with a creatinine clearance of 30 mL/min (low dose, 500/100 mg of amoxicillin/clavulanic acid three-times daily; high dose, 2000/400 mg of amoxicillin/clavulanic acid three-times daily). (b) Concentration versus time for a patient with a creatinine clearance of 50 mL/min (low dose, 500/100 mg of amoxicillin/clavulanic acid four-times daily; high dose, 2000/400 mg of amoxicillin/clavulanic acid four-times daily). (c) Concentration versus time for a patient with a creatinine clearance of 130 mL/min (low dose, 500/100 mg of amoxicillin/clavulanic acid six-times daily; high dose, 2000/400 mg of amoxicillin/clavulanic acid six-times daily). (d) Concentration versus time for a patient with a creatinine clearance of 190 mL/min (low dose, 500/100 mg of amoxicillin/clavulanic acid six-times daily; high dose, 2000/400 mg of amoxicillin/clavulanic acid six-times daily). Amoxicillin low dose, black broken line; clavulanic acid low dose, black continuous line; amoxicillin high dose, grey broken line; clavulanic acid high dose, grey continuous line.

oversimplification, but the data show that this approach is acceptable for drugs with low protein binding, such as amoxicillin (17% protein binding), although it is not accurate for more highly protein-bound drugs (G. Wong, S. Briscoe, S. Adnan, B. McWhinney, J. Ungerer, J. Lipman and J. A. Roberts, unpublished data). Moreover, we have only included 13 patients in this study, which may not be sufficient to describe the variability present in ICU patients. However, this small study still provides important guidance for dosing this drug in the ICU, given that data are presently not available.[17]

Conclusions

We found great variability in antibiotic clearance, which is not found in healthy volunteers, which points to the importance of individual dosing in ICU patients. We have shown that current dosing regimens of 1000/200 mg four-times daily or 2000/400 mg three-times daily for patients with low to normal creatinine clearance lead to sufficient pharmacokinetic exposure. However, patients with very high creatinine clearance need more frequent dosing or alternate dosing strategies to achieve the minimal pharmacodynamic target of 50% $fT_{>MIC}$ (8 mg/L), with little accumulation of

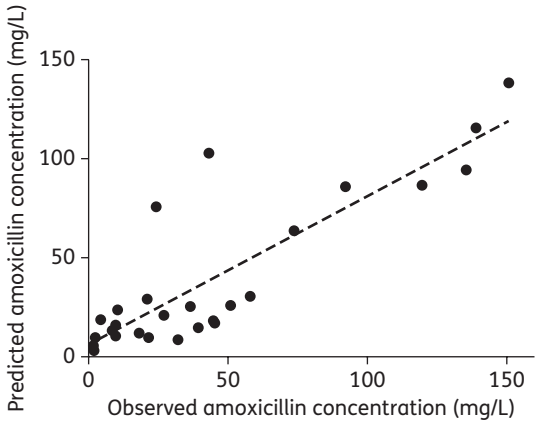

Figure 3. Observed amoxicillin concentrations versus predicted concentrations for 28 samples from 14 independent patients.

clavulanic acid. To achieve higher targets, such as 100% $fT_{>MIC}$, in patients with high creatinine clearance, the administration of higher doses as a prolonged infusion is necessary.

Funding

This work was supported by the Research Foundation Flanders. M. C. is funded by the Research Foundation Flanders (11E8512N) and has also received additional funding for a research stay (V403913N) at the Burns Trauma and Critical Care Research Centre, The University of Queensland, Brisbane. J. A. R. is funded by a Career Development Fellowship from the National Health and Medical Research Council of Australia (APP1048652).

Transparency declarations

None to declare.

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