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Pharmacokinetics of ceftazidime in serum and peritoneal exudate during continuous versus intermittent administration to patients with severe intra-abdominal infections

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Ceftazidime demonstrates time-dependent killing, which is maximal at 4 × or 5 × MIC for the organism, consequently continuous infusion (CI) has been proposed to ensure adequate ceftazidime concentrations for the entire course of therapy. Severe intra-abdominal infections (IAIs) require surgical or percutaneous drainage for management, and ceftazidime is frequently prescribed. Cardiovascular or metabolic changes and renal or liver dysfunction may alter drug pharmacokinetics during severe IAIs, and no data exist on concentrations of ceftazidime reached in the peritoneal fluid. The objectives here were to determine the pharmacokinetics of ceftazidime during continuous and intermittent administration in patients with severe IAIs, and to measure the concentrations of ceftazidime in the peritoneal exudate. Eighteen surgical patients with severe IAI and a creatinine clearance of >30 mL/min were studied. A non-randomized pilot study of six patients treated with CI alone was followed by a prospective, randomized comparative study of 12 patients. Pilot study patients received ceftazidime 1 g iv followed by a 4.5 g CI over 24 h. Randomized patients received either ceftazidime continuously as above or 1.5 g tds. Samples for pharmacokinetic analyses were collected on days 2 and 4. Ceftazidime concentrations were determined by high-performance liquid chromatography. CI resulted in a mean serum concentration >40 mg/L and a *T* > 4 × MIC for most pathogens encountered in severe IAIs for >90% of the course of therapy in both serum and peritoneal exudate. Eight-hourly administration resulted in *T* > 4 × MIC for most pathogens encountered in severe IAIs for >90% of the dosing interval, but in peritoneal exudate for only 44% of the dosing interval. During CI, AUCs in the peritoneal exudate were *c.* 60% of the concomitant serum AUCs. In critically ill surgical patients with severe IAIs, CI of ceftazidime resulted in more favourable concentrations in serum and peritoneal exudate than 8-hourly bolus infusion.

Introduction

Despite increased understanding of the pathophysiological principles, improved surgical techniques, the use of broad-spectrum antimicrobial agents and advances in life support facilities, severe intra-abdominal infections (IAIs) continue to have mortality rates between 30% and 76%.[1] These rates depend on a number of factors, including the magnitude of the systemic immune response, age, malnutrition, immune suppression, pre-existing disease, the source and extent of infection, delay to operation and pathogen virulence. Therefore, treatment must be optimized to improve outcome.

IAIs are almost always polymicrobial and comprise Gram-negative enteric bacteria, as well as obligate anaerobes. Antimicrobial chemotherapy should cover these microorganisms.[2] Antimicrobial selection pressure may change the spectrum of isolates to less susceptible Enterobacteriaceae and *Pseudomonas aeruginosa*,[3] against which ceftazidime is often the drug of choice.

The bactericidal activity of ceftazidime depends on the length of time that the concentration is above the MIC for

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the causative pathogen[4,5] and maximal killing is achieved at concentrations of 4 × or 5 × MIC.[6] Furthermore, ceftazidime does not exhibit a post-antibiotic effect against Gram-negative bacilli.[5] From a pharmacodynamic point of view therefore, continuous infusion (CI) may be preferable to intermittent dosing. CI eliminates the unnecessarily high peak and sub-MIC trough concentrations found with intermittent dosing.[7,8] From a pharmacokinetic point of view the advantages are less clear. A faster total body clearance after CI of piperacillin at high doses has been described.[9] Furthermore, drug concentration profiles in the peritoneal cavity after either method of administration have never been compared.

Cardiovascular and metabolic changes as well as renal and liver dysfunction can markedly alter the pharmacokinetics of ceftazidime during critical illness.[10–12] To our knowledge, the pharmacokinetics of ceftazidime in serum of critically ill patients with severe IAI has not been documented, nor have concentrations in peritoneal exudate been measured.

Materials and methods

The study protocol was approved by the medical ethics committee of Erasmus Medical Centre, Rotterdam. Informed consent was obtained from each patient or a first-degree relative (parents, partner or children).

Patient population

Patients who were admitted to the surgical intensive care unit (ICU) between January 1997 and May 1998 and who met the following criteria were eligible for enrolment in the study: over 18 years of age; severe IAI, defined as an IAI accompanied by a systemic inflammatory response, necessitating repeated laparotomies, open abdominal treatment or percutaneous drainage and intensive care support; suspected or proven Gram-negative infection.

Exclusion criteria were: known allergy to ceftazidime; creatinine clearance <30 mL/min and/or urinary output <10 mL/h over the preceding 12 h and/or haemofiltration or dialysis; severe granulocytopenia defined as <500 PMN/μL; APACHE II score ⩾30; use of selective decontamination of the digestive tract; causative pathogens resistant to ceftazidime.

All patients were classified according to the APACHE II score.[13] Use of concomitant drugs was documented and MICs of ceftazidime for the causative pathogens were determined by Etest (AB Biodisk, Solna, Sweden).

The following parameters were assessed: demography data including age, gender, weight and cause of the IAI; the number of surgical interventions and the amount of rinse fluid used in case of post-operative continuous lavage (i.e. maximum of 2 L 0.9% NaCl/24 h). Serum creatinine, alanine aminotransferase, aspartate aminotransferase, bilirubin, albumin, platelets and neutrophils were assessed daily. Creatinine clearance was estimated from the serum creatinine concentration using the Cockroft–Gault equation.[14] All adverse events were documented during the treatment period.

Study design

The study had two parts: the first was a prospective, non-randomized, non-comparative pilot study in which six patients received ceftazidime 1 g iv loading dose followed by a 4.5 g iv CI. This regimen was based on an assumed volume of distribution (V_d) of 300 mL/kg and a target concentration in serum of at least 40 mg/L. The second part was a prospective, randomized, comparative study in which 12 patients were randomized to receive either ceftazidime 1 g iv followed by a 4.5 g iv CI as above or ceftazidime 1.5 g iv bolus tds. Treatment was continued for up to 10 days.

Ceftazidime administration and dosage modulation

In patients with normal renal function, ceftazidime (Glaxo-Wellcome, Zeist, The Netherlands) was diluted in 250 mL 0.9% NaCl and continuously infused using an electronic pump (Ivac Medical System, Basingstoke, UK). The loading and intermittent bolus doses were prepared according to the manufacturer's guidelines and infused over 20 min. If creatinine clearance was between 49 and 30 mL/min, the total daily dosage was reduced to 2 g. If creatinine clearance dropped below 29 mL/min during the study period, the total daily dosage was reduced to 1 g.

Pharmacokinetics

Blood, peritoneal exudate and urine samples for the determination of ceftazidime concentrations were drawn on days 2 and 4. Peritoneal exudate cultures were taken before the start of therapy and repeated as considered necessary by the clinician.

Blood samples were taken from the non-infusion arm; during CI samples were drawn twice daily at intervals ranging from 8 to 12 h; during intermittent therapy, samples were drawn pre-dose ($t = 0$) and at 20 min, and 1, 2, 4 and 8 h after the start of the 20 min infusion. Blood was allowed to clot on ice for 20 min and centrifuged at 1500**g** for 10 min. The serum was stored at −70°C until analysis.

Peritoneal exudate was drawn from drainage catheters. During CI, samples were drawn at the same time as blood samples; after intermittent therapy, samples were taken 1 and 8 h after the start of the infusion. The total amount of peritoneal fluid drained was collected and a sample was taken for ceftazidime assay. Exudate was stored at −70°C until analysis.

Urine was collected over 24 h. The volume was measured and a sample was stored at −70°C for ceftazidime

assay. Ceftazidime concentrations were determined using high-performance liquid chromatography.[15] The lower limit of quantification was 0.4 mg/L in both serum and exudate and the method was linear up to 250 mg/L.

The primary descriptive parameters were area under the concentration curve (AUC_{0-24}), the serum elimination half-life ($t_{½}\beta$), the volume of distribution at steady state (V_{dss}), the total body clearance (CL) and concentrations reached in serum and exudate.

In the CI group, the AUC_{0-24} in serum and exudate was calculated as the mean concentration × 24 and the CL was calculated by dividing the infusion rate by the mean concentration over 24 h. In the intermittent therapy group, the AUC_{0-24}, $t_{½}\beta$ and V_{dss} in serum were estimated with the MWpharm program (Mediware, Groningen, The Netherlands) using a two-compartment model. AUC_{0-24} was calculated using the trapezoidal rule. CL was calculated using a non-compartmental equation [CL = dose/AUC (L/h)]. The AUC_{0-24} in exudate was estimated by multiplying the mean concentration over 8 h by 24.

The $AUC_{exudate}/AUC_{serum}$ ratio was calculated in those patients with both sample ports available. Time above the MIC ($T > MIC$) was estimated from the individual curves. The peritoneal clearance of ceftazidime was calculated by dividing the concentration of ceftazidime measured in the collected drain fluid by the total amount of ceftazidime infused in the same time period.

Statistical analysis

The Mann–Whitney test and Fisher's exact test were used as appropriate to determine differences between the groups; a $P < 0.05$ (two-tailed) was considered statistically significant. Correlation of ceftazidime clearance with creatinine clearance was determined using the Spearman correlation statistic. Patients were eligible for analysis if they had completed day 2 of the treatment period.

Results

Eighteen patients were enrolled, of whom 12 received continuous and six intermittent ceftazidime as part of an antimicrobial drug regimen. There were no statistical differences (data not shown) between the six CI patients of the pilot study and the six CI patients of the randomized study, therefore their data were pooled. In the CI group, eight patients received 4.5 g/24 h; one patient received 2 g/24 h; and three patients switched from 4.5 to 2 g/24 h during treatment. In the intermittent therapy group five patients received 1.5 g tds and one patient switched from 1.5 g tds to 1 g bd during treatment. Patients were treated concomitantly with other antibiotics directed against pathogens not susceptible to ceftazidime.

Demographics

The demographic characteristics of the study patients are summarized in Table 1. The groups were comparable as regards age, APACHE score and creatinine clearance. Severity of illness was reflected in a mean APACHE II score of 15 (= predicted mortality 24%) and an overall mortality on the ICU of 28%. The mean duration of treatment was 5 days.

Pharmacokinetics in serum

Serum ceftazidime concentrations were measured in 12 patients after CI and in six patients after intermittent therapy. The fitted curves for mean concentrations in serum versus time of both regimens are shown in Figure 1. The pharmacokinetic data on days 2 and 4 are shown in Table 2; only the randomized patients were compared statistically. The total body clearance, and subsequently the AUC_{0-24}, did not differ between groups. The mean steady state concentration in serum after CI was >40 mg/L.

Table 1. Patient demographics

	Continuous ($n = 12$)	Intermittent ($n = 6$)	P
Age (years)	62 (46–76)	64 (42–87)	
Male/female	7/5	4/2	
APACHE II score	16 (10–23)	14 (7–19)	0.3
Cause of peritonitis			
post-operative leakage	$n = 6$	$n = 3$	
pancreatitis	$n = 1$	$n = 2$	
gastrointestinal perforation	$n = 5$	$n = 1$	
Open abdomen technique	$n = 5$	$n = 3$	
Number of operations per patient (range)	1–10	2–5	
Overall mortality (on ICU) (%)	25	33	1.0
Creatinine clearance at inclusion (mL/min)	93 (36–215)	106 (59–160)	0.6

Where applicable, data are mean (range).

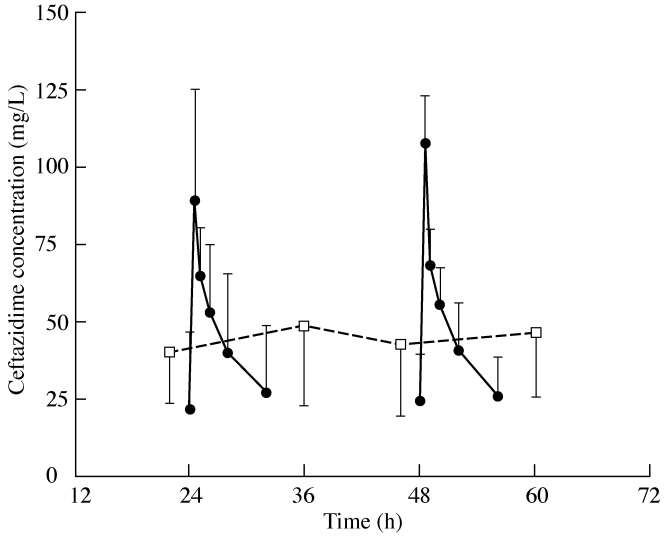

Figure 1. Concentration of ceftazidime in serum after continuous (n = 12; □) and intermittent (n = 6; ●) administration (mean ± S.D.).

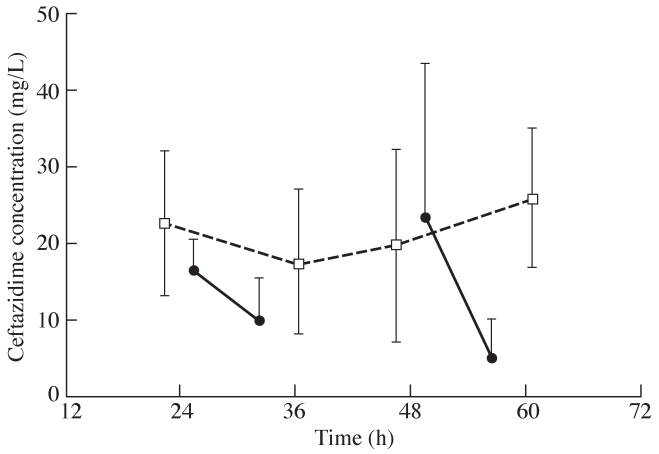

Figure 2. Concentration of ceftazidime in exudate after continuous (n = 9; □) and intermittent administration (n = 4; ●) (mean ± S.D.).

The lowest serum concentration during CI was 21.1 mg/L and the lowest trough concentration was 5.6 mg/L during intermittent therapy. The serum $t_{½}$ ranged widely. The V_{dss} approached the extracellular volume. Correlation between creatinine clearance and total body clearance of ceftazidime was 0.8 (R^2 = 0.64).

Pharmacokinetics in peritoneal exudate

Concentrations reached in peritoneal exudate were measured in nine patients after CI and in four patients after intermittent therapy. In three patients repeat laparotomy was cancelled; in two patients the intra-abdominal drains were removed before sample day 2. The fitted curves for mean concentrations in peritoneal exudate versus time of both regimens are shown in Figure 2.

Table 2 illustrates that, in peritoneal exudate, the calculated AUCs were higher in the CI group; on sample day 2 this difference was statistically significant. The mean $AUC_{exudate}/AUC_{serum}$ ratio varied between 56% and 64% during CI, and between 33% and 35% during intermittent therapy. This difference did not reach statistical significance. The lowest concentration in the peritoneal exudate during CI was 5.5 mg/L and the lowest trough concentration was 1 mg/L during intermittent therapy. Peritoneal clearance was low. Overall, 57% of a dose was found unchanged in urine after 24 h.

Pathogens

Table 3 shows the pathogens cultured and the MICs of ceftazidime. Twenty-six ceftazidime-susceptible Gram-negative pathogens were isolated from 18 patients. In one patient an intermediately susceptible (MIC ⩾ 16 mg/L) *Enterobacter cloacae* was cultured for which the antibiotic regimen was adjusted. Ceftazidime-resistant pathogens including anaerobes, coagulase-negative staphylococci, enterococci and *Candida* spp. were concomitantly treated with specific antimicrobial drugs.

Table 4 shows that the minimal concentrations in serum exceeded 4 × MIC for 100% of the dosing interval in both regimen groups. In exudate, this was 88% of the dosage interval in the intermittent therapy group. In addition, the CI regimen provided serum and exudate concentrations exceeding 16 mg/L (4 × MIC for a susceptibility breakpoint of 4 mg/L) for >90%, while in the intermittent therapy group this was only 44% in exudate. In the case of 4 × MIC for a susceptibility breakpoint of 8 mg/L, both regimens reached a serum concentration of approximately 70% of the dosage interval; five of the 12 CI patients and six of the six patients on intermittent therapy had concentrations <32 mg/L. In exudate both regimens were insufficient for this target concentration. No allergic reactions or elevated liver enzymes were observed during the study period.

Discussion

This study demonstrated that, from a pharmacokinetic and pharmacodynamic point of view, CI of ceftazidime results in more favourable concentrations in serum than intermittent infusion of the same daily dosage to critically ill patients with severe IAIs. Animal models suggest that maximal efficacy of ceftazidime is achieved when concentrations in serum are maintained above 4 × MIC for at least 60% of the dosing interval for Enterobacteriaceae.[16] In the case of a *Pseudomonas* infection, sustained concentrations above at least 4 × MIC are recommended.[6] Since the ceftazidime MIC_{90} for *Pseudomonas* is 8 mg/L in our institution (unpublished data from blood cultures in ICU patients), a

Table 2. Pharmacokinetic parameters of ceftazidime in serum and peritoneal exudate

	Day 2			Day 4		
PK parameter	CI[a]	IB[b]	P[c]	CI[a]	IB[b]	P
Serum						
AUC_{0-24} (mg·h/L)	1131 (505–2230)	1064 (505–1950)	0.5	1098 (581–2233)	1166 (644–1496)	0.6
C_{mean} (mg/L)	47.1 (21.1–92.9)			45.1 (24.2–93.1)		
C_{max} (mg/L)		88.7 (58.3–124.8)			104.4 (94.6–127.8)	
C_{trough} (mg/L)		19.4 (5.6–68.4)			23.7 (7.1–41.3)	
V_{dss} (L/kg)		0.279 (0.146–0.443)			0.240 (153–339)	
$t_{½}\beta$ (h)		4.2 (1.3–12.3)			3.0 (1.3–3.9)	
CL (L/h)	4.1 (1.4–8.9)	5.1 (2.3–8.9)	0.2	4.2 (1.6–7.7)	4.0 (2.0–7.0)	0.3
renal excretion (%)	59 (18–127)	51 (23–81)	0.5	59 (18–102)	69 (39–74)	0.5
Exudate						
AUC_{0-24} (mg·h/L)	522 (132–838)	316 (204–445)	0.01	637 (420–940)	346 (73–728)	0.1
C_{mean} (mg/L)	21.7 (5.5–34.9)			26.6 (17.5–39.2)		
$C_{1\,h}$ (mg/L)		15.9 (10.3–20.0)			24.7 (5.4–52.2)	
$C_{8\,h}$ (mg/L)		11.2 (5.2–17.1)			6.8 (1.0–10.8)	
Clearance by drainage (%)	1.2 (0.6–1.5)	0.75 (0.5–1.6)	0.7	0.75 (0.4–0.9)	0.4 (0.3–0.9)	0.6
Volume exudate (mL)	1600 (200–3200)	1800 (100–2800)	0.8	1600 (100–4900)	1600 (200–3800)	0.6
$AUC_{exudate}/AUC_{serum}$ (%)	56 (19–112)	35 (19–45)	0.09	64 (27–94)	33 (5–61)	0.15

Where applicable, data are mean (range).
[a]CI for serum, $n = 12$; CI for exudate, $n = 9$.
[b]IB for serum, $n = 6$; IB for exudate, $n = 4$.
[c]Only the randomized patients are compared statistically.

Table 3. Pathogens cultured from the peritoneal exudate and their ceftazidime MIC

Pathogen	*n* (%)	MIC (mg/L)[a]
Escherichia coli	11 (42)	0.25 (0.125–2)
P. aeruginosa	9 (34)	2 (2–4)
Klebsiella oxytoca	2 (8)	0.19–0.25
Proteus mirabilis	2 (8)	0.125
Stenotrophomonas maltophilia	1 (4)	1.5
Citrobacter sp.	1 (4)	0.5

[a]Where applicable, data are mean (range).

ceftazidime concentration of at least 32 mg/L would be required with an empirical regimen until the causative pathogen had been isolated and the MIC determined. In this study, CI of 4.5 g/24 h after a loading dose of 1 g resulted in a mean steady-state concentration in serum >32 mg/L. However, concentrations ranged widely, with five of the 12 CI patients having concentrations <32 mg/L during therapy. The intermittent bolus regimen of 1.5 g tds resulted in a very high mean peak concentration in serum that, generally, would not add to the bactericidal activity of ceftazidime, while the mean trough concentration in serum fell well below 32 mg/L. All six patients had serum concentrations <32 mg/L during therapy.

As critically ill patients show highly variable drug pharmacokinetics, the length of time that the serum concentrations remained above the target concentration of 32 mg/L for individual patients is important. In our study population, concentrations $\geqslant$ 32 mg/L were reached only for approximately 70% of the dosing interval for both regimens. When the concentration falls below the threshold concentration regrowth of pathogens and development of resistance can occur. Therefore, a higher ceftazidime dosage is indicated in cases of *Pseudomonas* infection for which the MIC is 8 mg/L.

Other studies investigating CI of ceftazidime in critically ill patients found variable serum concentrations depending on the total body clearance. In critically ill medical patients, a mean steady state serum ceftazidime concentration of 30 mg/L was reached with an infusion of 3 g/24 h, while the total body clearance was approximately 4 L/h.[10] In patients with nosocomial pneumonia using the same regimen (3 g/24 h), the total body clearance was twice as high ($\pm$ 8 L/h), and therefore a mean steady state concentration of only 17 mg/L was reached.[17] Lipman *et al.*[12] showed that ceftazidime CI 6 g/24 h was needed in (unspecified) critically ill patients with a total body clearance of approximately 6 L/h to maintain a serum concentration of 40 mg/L.

Antimicrobial drugs must act at the site of infection. Thus, in the case of severe IAIs, the concentrations reached in the peritoneal exudate are relevant. In this study, CI resulted in a mean steady state concentration at the site of infection > 24 mg/L, while intermittent dosing resulted in much lower mean maximum and trough concentrations measured in the peritoneal exudate. This resulted in the $T >$ MIC at the site of infection during CI being more favourable. However, both dosing regimens failed to achieve 32 mg/L, suggesting that a higher dosage might improve bacteriological efficacy.

AUCs in the peritoneal exudate were approximately 60% of the concomitant serum AUCs after CI. Since the binding of ceftazidime to plasma protein is only 17%,[18] this can only partly explain this discrepancy. Another explanation would be incomplete passage through the blood–peritoneum barrier. Corbett *et al.*[19] found that the ceftazidime concentration in normal peritoneal fluid of patients undergoing elective abdominal surgery was only 62% of the concomitant serum level. In our patients, rapid clearance through the drains may have prevented equilibration. Alternatively, the peritoneal fluid may have been diluted by continuous lavage. The $AUC_{exudate}/AUC_{serum}$ ratio after intermittent therapy was lower (30%) than after CI, but this did not reach statistical significance. The difference between continuous and intermittent administration could

Table 4. Time above the MIC in serum and peritoneal exudate

		Continuous infusion (%)	Intermittent bolus (%)
$T > 4\times$ $MIC_{(actual)}$[a]	serum	100	100
	exudate	100	88
$T >$ 16 mg/L	serum	100	90
	exudate	92	44
$T >$ 32 mg/L	serum	67	69
	exudate	45	6

%, percentage of the dosing interval in which the concentrations in serum or exudate exceeded the indicated concentrations.

[a]$MIC_{(actual)}$ is the MIC for the individual patient's isolates; 16 mg/L and 32 mg/L are 4 $\times$ MIC for isolates showing reduced susceptibility (MIC 4–8 mg/L).

be explained by the method of sampling. If the time to reach the peak concentration in the peritoneal exudate is longer than 1 h, we measured a submaximal concentration and therefore underestimated the AUC. However, Mouton *et al.*[20] measured concentrations reached in blister fluid after CI and intermittent infusion in healthy volunteers and found equal peak concentrations at 1 h with both regimens.

Compared with data from healthy volunteers (V_d = 180 mL/kg; $t_{½}$ = 1.6 h; CL = 8.5 L/h),[20,21] the serum pharmacokinetic parameters in this study revealed an increased volume of distribution and a decreased total body clearance resulting in an increased $t_{½}$. In addition, the data showed considerable variance. Comparable variability of the pharmacokinetic profile has been observed in critically ill patients with pneumonia.[10–12,17] Since ceftazidime is not metabolized, has low protein binding and is almost entirely eliminated by glomerular filtration, the variability in clearance depends mainly on renal function[22] and this varies widely among the critically ill. Approximately 30% of all patients with severe sepsis develop renal failure.[23] In addition, critical illness can be associated with a significant increase in the volume of distribution.[11]

Variable pharmacokinetics result in variable concentration profiles with unpredictable low trough concentrations after intermittent dosing of ceftazidime.[24] Using CI it is easier to sustain a target concentration. Based on these data, a population model for patients with complicated IAIs can be made. Routinely available clinical variables such as bodyweight, age, gender and serum creatinine can be used to predict ceftazidime clearance.[25] Using information about the individual pharmacokinetic profile and the MIC for the causative pathogen, the optimal dose of ceftazidime can be determined. This goal-oriented dosing of ceftazidime might result in higher bacteriological cure rates. Extrapolating the data available to our situation (V_d = 260 mL/kg, CL 4 L/h and 60% penetration), the dose of ceftazidime must be between 1.5 and 4.5 g/24 h after a loading dose of = 1 g to achieve an optimal concentration in peritoneal exudate for pathogens for which the MIC is 2–6 mg/L. In the case of peritonitis caused by *Pseudomonas* for which the MIC is 8 mg/L, the dosage of ceftazidime must be at least 6 g/24 h after a loading dose of 1 g. In critically ill patients with a total body clearance >4 L/h,[17,24] the dosage must be even higher. Although ceftazidime is a drug with low toxicity, mild hypersensitivity being the most common side effect,[26] dosage regimens of >80 mg/kg/24 h have not been tested in humans.

We conclude that from a pharmacokinetic and pharmacodynamic point of view, CI of ceftazidime results in more favourable concentrations in serum and peritoneal exudate compared with intermittent administration to critically ill surgical patients with complicated IAIs. In addition, with CI, serum concentrations can be predicted, allowing a more accurate dosage adjustment. Since the $AUC_{exudate}$/AUC_{serum} ratio after CI was approximately 60%, higher dosage may be necessary when treating patients with those pathogens for which MICs are higher (e.g. *Pseudomonas*).

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