Journal of Antimicrobial Chemotherapy (2009) **63**, 564–567
doi:10.1093/jac/dkn522
Advance Access publication 23 January 2009

JAC

Plasma and peritoneal concentration following continuous infusion of cefotaxime in patients with secondary peritonitis

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Received 18 June 2008; returned 9 September 2008; revised 21 November 2008; accepted 7 December 2008

***Objectives*: The aim of this study was to determine the steady-state plasma and peritoneal concentrations of cefotaxime and its metabolite desacetyl-cefotaxime administered by continuous infusion to critically ill patients with secondary peritonitis.**

***Patients and methods*: In 11 patients, a continuous infusion of 4 g/24 h of cefotaxime following a bolus of 2 g was evaluated. Plasma and peritoneal levels of cefotaxime and desacetyl-cefotaxime were measured at steady state on days 2 and 3 (plasma) and on day 3 (peritoneal) by HPLC. Results are expressed as means ± SD.**

***Results*: Total and unbound plasma levels of cefotaxime were 24.0 ± 21.5 and 20.3 ± 19.8 mg/L on day 2 and 22.1 ± 20.7 and 18.9 ± 19.2 mg/L on day 3, respectively. Total and unbound levels of cefotaxime in the peritoneal fluids were 16.2 ± 11.5 and 14.3 ± 10.4 mg/L, respectively. The unbound fraction of plasma cefotaxime was 81.8 ± 5.9% on day 2 and 82.6 ± 7.7% on day 3, and the unbound fraction at the peritoneal site was 87.0 ± 5.5% on day 3. Total and unbound plasma levels of desacetyl-cefotaxime were 9.0 ± 8.1 and 8.4 ± 8.1 mg/L on day 2 and 7.6 ± 7.6 and 7.2 ± 7.6 mg/L on day 3, respectively. Total and unbound levels of desacetyl-cefotaxime in the peritoneal fluids were 11.9 ± 11.5 and 10.9 ± 10.8 mg/L, respectively. The MICs for the enterobacteria recovered ranged from 0.016 to 0.25 mg/L.**

***Conclusions*: Continuous infusion of 4 g/24 h of cefotaxime provided a peritoneal concentration >5× MIC for the recovered Enterobacteriaceae and the susceptibility breakpoint of cefotaxime for facultative Gram-negative bacilli.**

Keywords: human, critically ill patients, high performance liquid chromatography, protein binding

Introduction

In secondary peritonitis, the choice of initial antibiotic therapy is clearly empirical, but must cover Enterobacteriaceae (in particular, *Escherichia coli*) and the anaerobic flora for community-acquired peritonitis, and must be adapted to the local ecology in cases of post-operative peritonitis.[1,2] In this context, β-lactams are frequently used alone or in association with a drug active against anaerobic strains.

β-Lactams are time-dependent antibiotics, and the time above the MIC is the pharmacokinetic/pharmacodynamic parameter that correlates with the therapeutic efficacy.[3] A percentage of the time above MIC superior to 40% is classically required, and in critically ill patients, a percentage equal to 100% is recommended.[4] In this context, continuous infusion of various β-lactams is an attractive way of administration allowing a stable concentration at the steady state, usually at a level superior to 4–5 × MIC.[3]

Cefotaxime is a cephalosporin active against facultative Gram-negative bacilli (GNB), in particular against *E. coli*, and is usually administered by intermittent infusion in intra-abdominal infections.[2] Its main metabolite, desacetyl-cefotaxime, possesses antibacterial activity, but it is less active than cefotaxime.[5]

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The objective of this study was to determine the steady-state plasma and peritoneal concentrations of cefotaxime and desacetyl-cefotaxime administered by continuous infusion to critically ill patients with intra-abdominal infections and to compare these concentrations with the susceptibility of the recovered GNB.

Patients and methods

This prospective observational study was performed in the surgical intensive care unit of a university hospital over a period of 10 months (from 1 December 2006 to 1 September 2007). As surgical drainage was required to sample the peritoneal fluid, this series of patients was not consecutive. The local Ethics Committee ('Comité de Protection des Personnes' of Rennes) approved the study and waived the need for written consent because no additional sample was necessary (date of agreement: 9 May 2006).

Adult patients more than 18 years old who had secondary peritonitis, defined as diffuse peritonitis originating from a defect in the abdominal viscus, operated and drained, and in whom treatment by cefotaxime was indicated were eligible. Non-inclusion criteria were limited to pregnant women, patients known to have an allergy to cefotaxime and/or who had at admission a creatinine clearance (CL_{CR}) <30 mL/min (Cockroft and Gault formula).

Before the beginning of this study, the stability of cefotaxime (Sanofi Aventis Laboratory, Paris, France) was evaluated at room temperature (24°C) during a 24 h period (4 g of cefotaxime diluted in 50 mL of serum saline). This experiment was performed in triplicate. Cefotaxime solutions were stable >93% at 24 h (data not shown).

Once inclusion and non-inclusion criteria had been checked, the following data were recorded: age, gender, weight, height and body surface area (Gehan and George formula). Severity was assessed by Acute Physiology and Chronic Health Evaluation II (APACHE II) score and the number and intensity of organ dysfunction by the Sequential Organ Failure Assessment (SOFA) score. The patients received an intravenous loading dose of 2 g of cefotaxime over a 10 min period, followed by a continuous infusion via an automatic pump (Fresenius Vial, Module MUP MS/EC; Brézins, France) of 4 g of cefotaxime in 50 mL of serum saline administered over 24 h. This dose was chosen in accordance with the international guidelines (intermittent infusion 3–6 g/day) and by analogy with ceftazidime, another cephalosporin that possesses pharmacological properties close to cefotaxime and in which the continuous infusion at a dose of 4 g/day is well validated.[6] As cefotaxime is not active against all anaerobic strains, in particular *Bacteroides fragilis* (an important pathogen in peritonitis), metronidazole was given at a dose of 500 mg three times a day. The plasma levels of cefotaxime and desacetyl-cefotaxime (total and unbound fraction) were obtained at steady state on days 2 and 3. Cefotaxime and desacetyl-cefotaxime levels were determined from the peritoneal fluid exteriorized by surgical drainage (vacuum suction system using a redon catheter or latex drainage tube). In all cases, fresh peritoneal fluid (≤1 h) was removed simultaneously to the plasma on day 3. All the samples were obtained at the end of the perfusion. When a significant contamination of blood in the peritoneal fluid was observed (red cells >5 per field at magnification ×10), the sample was not analysed. On day 2, serum and 24 h urinary creatinine were measured, and CL_{CR} was calculated. The serum proteins (normal values 60–80 g/L) and albumin (normal value >40 g/L) were also measured on day 2.

Cefotaxime and desacetyl-cefotaxime were determined by HPLC with ultraviolet detection at 230 nm. The analytical method has been validated for simultaneous quantification of 11 β-lactams and has been routinely used for several years in the laboratory. Cefotaxime sodium salt was purchased from ICN Biomedical (Orsay, France), and desacetyl-cefotaxime was a gift from Sanofi Aventis (Frankfurt, Germany). Free plasma and peritoneal fractions of cefotaxime and its metabolite were separated by ultrafiltration using Centrifree® (Millipore Corporation, Bedford, MA, USA). All molecules were extracted by precipitation with acetonitrile. Separation was achieved with an Atlantis® dC18 column (5 μm, 4.6 × 150 mm, Waters, Milford, MA, USA) coupled with a Waters Atlantis® dC18 guard column (5 μm, 4.6 × 20 mm). The mobile phase consisted of a linear gradient of ortho-phosphoric acid solution adjusted to pH 2 and acetonitrile from 7% to 22%, with a flow rate of 2 mL/min. Retention time was 4 min for desacetyl-cefotaxime and 7.2 min for cefotaxime. This method is accurate and reproducible (coefficient of variation <5%), allowing quantification of plasma levels of cefotaxime and desacetyl-cefotaxime from 1 to 250 mg/L without the interference of other common drugs.

The MIC for the GNB was determined by the Etest (AB Biodisk, Solna, Sweden). Enterobacteria were considered susceptible to cefotaxime if MICs were ≤1 mg/L, resistant if MICs were >2 mg/L and intermediate if MICs were between these two concentrations, according to the recommendations of the French Society for Microbiology (http://www.sfm.asso.fr/).

Statistical analysis was performed using SPSS software 10.0 (SPSS Inc., Chicago, IL, USA). Data are expressed as means ± SD unless otherwise indicated.

Results

During the period of study, a total of 11 patients (3 women and 8 men) were included. Age was 60 ± 20 years, weight was 70 ± 16 kg, height was 167 ± 5 cm and body surface area was 1.8 ± 0.2 m^2. The severity assessed by APACHE II score was 17 ± 6. SOFA score was 6 ± 3. Four patients received norepinephrine for septic shock. The hospital mortality was 27%.

On day 2, CL_{CR} was 89 ± 57 mL/min (range from 34 to 232 mL/min), and the values of serum proteins and albumin were 45 ± 7 and 17 ± 5 g/L, respectively.

Microorganisms recovered from the peritoneal samples were: *E. coli* ($n = 6$), *Klebsiella pneumoniae* ($n = 1$), *Serratia marcescens* ($n = 1$), *Enterococcus* spp. ($n = 4$), *Staphylococcus aureus* ($n = 1$), *Clostridium* sp. ($n = 1$) and *Candida albicans* ($n = 1$). The MIC for the enterobacteria recovered ranged from 0.016 to 0.250 mg/L.

Plasma levels of cefotaxime and desacetyl-cefotaxime on days 2 and 3 are reported in Tables 1 and 2. Plasma and peritoneal cefotaxime were essentially present in an unbound form (Table 1). The levels of cefotaxime and desacetyl-cefotaxime in the peritoneal fluids are presented in Tables 1 and 2.

A significant negative correlation was found between the plasma levels of cefotaxime and the CL_{CR} on day 2 ($r = -0.84$), whereas no significant correlation was found between the plasma levels of cefotaxime and weight, severity assessed by APACHE II or body surface area.

Discussion

This study showed that, in critically ill patients with severe intra-abdominal infections, continuous infusions of cefotaxime at a dose of 4 g/day provided plasma and peritoneal levels of cefotaxime (total and unbound fractions) far above the MIC for the GNB recovered from the surgical peritoneal samples.

Table 1. Plasma and peritoneal concentrations and free fraction of cefotaxime (CTX)

	Day 2 serum concentration of CTX			Day 3 serum concentration of CTX			Peritoneal concentration of CTX			
Patient	total (mg/L)	unbound (mg/L)	free fraction (%)	total (mg/L)	unbound (mg/L)	free fraction (%)	total (mg/L)	unbound (mg/L)	free fraction (%)	Unbound peritoneal/ plasma CFX
1	33.2	27.7	83.4	30.1	26.8	89.0	28.0	24.9	88.9	0.93
2	16.1	14.0	87.0	10.4	9.2	88.5	10.5	8.3	79.0	0.90
3	8.7	6.2	71.3	12.2	8.4	68.9	7.3	6.1	83.6	0.73
4	15.5	12.0	77.4	14.6	11.6	79.5	12.4	10.3	83.4	0.89
5	21.9	17.9	81.7	18.8	13.9	73.9	19.1	17.1	89.5	1.23
6	13.9	12.4	89.2	12.0	11.0	91.7	10.7	9.4	87.9	0.85
7	14.4	10.9	75.7	16.5	12.6	76.4	10.0	8.4	84.0	0.67
8	25.0	20.4	81.6	22.6	19.4	85.8	15.0	14.1	94.0	0.73
9	8.7	6.8	78.2	7.9	6.1	77.2	6.3	5.1	81.0	0.84
10	85.0	77.0	90.6	81.6	74.1	90.8	45.8	40.9	89.3	0.55
11	21.2	17.8	84.0	16.4	14.3	87.2	13.4	13.0	97.0	0.91
Mean ± SD	24.0 ± 21.5	20.3 ± 19.8	81.8 ± 5.9	22.1 ± 20.7	18.9 ± 19.2	82.6 ± 7.7	16.2 ± 11.5	14.3 ± 10.5	87.1 ± 5.5	0.84 ± 0.18

Table 2. Plasma and peritoneal concentrations and free fraction of desacetyl-cefotaxime (DCTX)

	Day 2 serum concentration of DCTX			Day 3 serum concentration of DCTX			Peritoneal concentration of DCTX			
Patient	total (mg/L)	unbound (mg/L)	free fraction (%)	total (mg/L)	unbound (mg/L)	free fraction (%)	total (mg/L)	unbound (mg/L)	free fraction (%)	Unbound peritoneal/ plasma DCTX
1	8.8	7.5	85.2	5.4	5.3	98.1	13.6	12.8	94.1	2.42
2	11.4	11.1	97.4	8.1	7.9	97.5	11.2	10.8	96.0	1.37
3	2.4	1.7	70.8	2.0	1.9	95.0	2.0	1.7	83.3	0.89
4	6.7	6.1	91.0	5.4	5.1	94.4	7.6	6.5	84.9	1.27
5	12.3	11.2	91.1	9.6	8.2	85.4	16.7	15.3	91.6	1.87
6	3.0	2.7	90.0	2.1	1.8	85.7	4.9	4.5	91.2	2.50
7	6.2	5.7	91.9	5.9	4.9	83.1	6.3	5.7	90.5	1.16
8	8.7	8.4	96.6	7.6	7.3	96.1	12.3	10.5	85.3	1.44
9	2.4	1.9	79.2	2.2	1.9	86.4	3.1	2.6	83.9	1.37
10	31.1	30.8	99.0	29.3	28.9	98.6	43.9	41.0	93.4	1.42
11	6.1	5.8	95.1	6.2	5.7	91.9	8.9	8.4	94.4	1.47
Mean ± SD	9.0 ± 8.1	8.4 ± 8.1	89.9 ± 8.5	7.6 ± 7.6	7.2 ± 7.6	92.0 ± 5.8	11.9 ± 11.5	10.9 ± 10.9	89.9 ± 4.7	1.56 ± 0.5

Despite being a well-established drug in intra-abdominal infections, the peritoneal diffusion of cefotaxime has not been studied in more seriously infected patients. Nevertheless, the knowledge of the pharmacokinetic profile of antimicrobial agents is crucial in critically ill patients because several pathophysiological conditions alter the pharmacokinetics of these agents.[7]

Continuous infusion of β-lactams is widely used in intensive care patients, but few data are available for cefotaxime. Buijk *et al.*[8] have compared the pharmacokinetics of cefotaxime during continuous and intermittent infusions in serum and bile in liver transplant patients and found that serum concentration may be insufficient with intermittent infusion during the reperfusion phase. Despite a significant inter-patient variation, we found that a continuous infusion of cefotaxime at 4 g/24 h provided permanent mean plasma and peritoneal levels of cefotaxime $>4-5\times$ MIC for the bacteria recovered from the peritoneal samples. Moreover, the mean plasma and peritoneal concentrations were above the susceptibility breakpoint for cefotaxime (1 mg/L).

The close relationship between the unbound plasma and peritoneal cefotaxime concentrations is not surprising as the peritoneum membrane is complex, but acts as a semi-permeable barrier leading to equilibrium between the plasma and peritoneal unbound cefotaxime. Nevertheless, the peritoneal concentration of cefotaxime was lower than the corresponding concentration in plasma, whereas the peritoneal concentration of the metabolite was higher than that in the plasma, suggesting a local degradation of cefotaxime. Such a finding has been previously reported by Heim *et al.*[9] with cefotaxime in anuric patients and by Karjagin *et al.*[10] with meropenem. We have performed an additional *in vitro* stability study by adding known concentrations of cefotaxime into the peritoneal fluid of three patients and found in comparison with serum saline (at 37°C and at 2, 4, 6, 10 and 24 h) a more rapid degradation of cefotaxime in the peritoneal fluid ($0.7\ \text{mg/L}\cdot\text{h}^{-1}$; value for serum saline $= 0.4\ \text{mg/L}\cdot\text{h}^{-1}$) (data not shown). The mechanism of such degradation remains to be elucidated.

In conclusion, our study suggests that despite wide inter-patient variation, continuous administration of 4 g/24 h of cefotaxime provides a peritoneal concentration exceeding the MIC for the Enterobacteriaceae recovered and the susceptibility breakpoint for GNB.

Funding

No funding of any kind has been received for this research.

Transparency declarations

None to declare.

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