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Ceftobiprole: pharmacokinetics and PK/PD profile

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ABSTRACT

Ceftobiprole shows many similar pharmacokinetic properties to other cephalosporins, except for not being orally bioactive, and that it is administered by IV infusion as the prodrug ceftobiprole medocaril, which is subsequently hydrolyzed in the blood into the active molecule. Distribution focus in extracellular fluid and active antibiotic concentration has been proven in different corporal tissues using dosing regimen of 500 mg intravenous infusion over 2 h every 8 h. Ceftobiprole is eliminated exclusively into the urine, thus the reason why dose adjustment is required for patients with moderate or severe renal impairment, or increased creatinine clearance. However, there is no need for dose adjustments related with other comorbidities and patients' conditions such as age, body weight. Although considering distribution features, molecular weight and dose fraction, increase dosing regimen might be necessary in patients using renal replacement therapy. The half-life of ceftobiprole is more than 3 h, allowing to easily reach optimal PK/PD parameters with the infusion time of 2 h, using the usual dosing regimen.

Keywords: Ceftobiprole, clinical pharmacokinetics, PK/PD relationships

INTRODUCTION

The on-going and rapid development of antibiotic resistance of different pathogens is now a growing concern leading to potential risks for patients. The specific case of Gram-positive bacteria is not impervious to this situation, for which reason the availability of a new drug that allows for specifically directed treatment toward resistant forms is welcome.

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Ceftobiprole, a beta-lactam antibiotic belonging to the cephalosporin group, is the latest inclusion into the select group of active drugs against these types of bacteria, hence the interest in practically describing the primary pharmacokinetic and pharmacokinetic/pharmacodynamic (PK/PD) characteristics in order to achieve more efficient use of this drug.

PHARMACOKINETICS

General Information. Ceftobiprole is a cephalosporin that is administered in the form of the prodrug ceftobiprole medocaril, which is rapidly converted in the plasma, likely through esterases, to its active fraction; ceftobiprole. The approved dose is 500 mg every 8 hours administered intravenously as a 120 minute infusion. This cephalosporin presents linear pharmacokinetics after a single dose and multiple doses between 125 and 1,000 mg [1-3]; furthermore, the pharmacokinetics are independent of the duration of administration [4]. The state of equilibrium is achieved during the first day [5], there is no drug accumulation when administered every 8 h in patients with normal kidney function [4], which is fully justified considering the elimination half-life of about 3 h. Table 1 [6] shows the pharmacokinetic parameters obtained after administration of the approved dose of 500 mg in a 2-hour infusion to healthy volunteers.

Systemic exposure defined by the area under the curve during the dosing interval ($AUC_{0-\tau}$), and maximum plasma concentration (Cmax) reached on day 5 were similar to those determined on day 1 (AUC 102 ± 11.9 and 90 ± 12.4 mg h/l, respectively; Cmax, 33 ± 4.83 and 29.2 ± 5.52 mg/l, respectively).

The renal clearance and systemic clearance values did not change either in relation to the day of administration, kidney clearance for the first day being 4.28 ± 0.57, and 4.08 ± 0.72 l/h on day 5, resulting in total clearance on these same days of 4.98 ± 0.58 and 4.89 ± 0.69 l/h, respectively.

Table 1 Single dose ceftobiprole. Pharmacokinetic parameters [2, 4, 6]

Dose (mg)	500
Perfusion time (hours)	2
Cmax (mg/l)	29.2 ± 5.5
AUC0-∞ (mg h/l)	104 ± 13
t½ (h)	3.1 ± 0.3
Vd (l)	21.7 ± 3.3
Plasma protein binding (%)	16
Cl_t (l/h)	4.8 ± 0.7
Cl_r (l/h)	4.1 ± 0.7
Active urinary excretion (%)	83.1 ± 9.1

Cmax: maximum plasma concentration
$AUC_{0-\infty}$: extrapolated area under the curve
t½: excretion half-life
Vd: volume of distribution
Cl_t: total clearance
Cl_r: kidney clearance

The drug elimination half-life was 3.3 ± 0.3 h the first day and 3.1 ± 0.3 h on day 5 [4, 6].

Distribution. A volume of distribution of 21.7 ± 3.3 l and 15.5 ± 2.33 l on day 1 and day 5, respectively, has been reported. This volume of distribution is similar to extracellular volume for an adult patient, information consistent with that of the vast majority of beta-lactam antibiotics in general and cephalosporins in particular [6]. The plasma protein binding of ceftobiprole is very low, only 16% of it is albumin-bound [5], which facilities this drug's penetration of several body tissues.

Ceftobiprole's penetration of soft tissues, including adipose, and bone tissue, has been studied, following the administration of a single dose of 500 mg of ceftobiprole over a 2-h infusion in healthy volunteers, using microdialysis measures. Striated muscle penetration of 69% and adipose tissue penetration of 49% were determined [7]. In adult patients who received 500 mg ceftobiprole in an IV infusion before undergoing hip prosthesis surgery, ceftobiprole exposure in cortical bone was 3.5 times higher than what was determined for spongy bone [8]. The ratio between tissue and plasma concentrations was 0.22 for cortical bone and 0.06 for spongy bone (0.15-0.3) [9]. The PK/PD study performed using the collected data confirmed that the likelihood of reaching a value of T > MIC of 30-40% was >90% in all tissues evaluated when MIC was 2 mg/l [10].

The clinical relevance of this PK/PD profile has been shown in relation to the differences evaluated in a rabbit tibia infection model in which the administration of this drug for 4 weeks reduced the bacterial count to below detectable limit in all animals treated, while it was reduced by 73% in animals treated with vancomycin or linezolid [11].

The penetration of ceftobiprole was evaluated in bronchoalveolar lavage (BAL) fluid in healthy subjects following the administration of 4 conventional doses of ceftobiprole [12], verifying that the BAL concentration was lower than in plasma 8h after starting the infusion, reporting a value of 25.5% in relation to BAL/plasma concentration.

Excretion. Ceftobiprole is predominantly excreted in the urine [4, 6] as indicated by total clearance values, which coincide with kidney clearance. Approximately 80-90% of the drug administered may be recovered unaltered in the urine [1, 4]. Excretion occurs primarily through glomerular filtration and it appears that active tubular secretion is not involved [4], therefore, no interactions are expected in the kidney excretion of the drug [13]. This circumstance justifies the fact that the pharmacokinetics of ceftobiprole are modified in patients with kidney failure [14]. At the same time, it justifies the limited presence of ceftobiprole in the intestinal lumen, which explains why active drug concentrations have not been detected in the faeces of healthy subjects who received IV infusions of 500 mg/8 h ceftobiprole for 7 days. This characteristic may account for the rare incidence of effects on the intestinal flora, as well as not detecting *C. difficile* or its toxin in ceftobiprole-treated patients [15].

PHARMACOKINETICS IN SPECIAL SITUATIONS

Patients with kidney failure. Ceftobiprole is almost entirely passively excreted unchanged through glomerular filtration, it is therefore important to know the impact that the presence of kidney failure could have on pharmacokinetics and the corresponding dose adjustment.

To that end, a study was conducted in which the pharmacokinetic parameters of administering a single 250-mg dose in one 30-minute infusion in healthy volunteers and subjects with different degrees altered kidney function were compared [14, 16].

As shown in table 2, kidney clearance for ceftobiprole was reduced in a significant manner in patients with moderate to severe kidney failure (80% and 91%, respectively) when compared with normal kidney function. Systemic clearance and kidney clearance showed a linear relationship with patients' creatinine clearance (CrCl) (correlation coefficient of 0.98 in both cases), confirming that required dose adjustment according to kidney function may be predicted based on creatinine clearance [14].

A study conducted on patients with terminal kidney failure requiring dialysis [14] demonstrated that systemic exposure expressed as a value of area under the curve between 0 and infinity ($AUC_{0-\infty}$), was 3.2 times higher in subjects with altered kidney function than in healthy subjects when analysed pre-dialysis, and approximately 7 times higher when analysed post-dialysis. This finding is explained through the reduction of systemic clearance with subsequent increase in half-life. It has been estimated that ceftobiprole extraction during a 4-h

Table 2 **Ceftobiprole. Pharmacokinetic parameters (mean ± standard deviation) in patients with kidney failure [14, 16]**

Degree of kidney failure. Creatinine Clearance (CrCl ml/min). Dose: 250 mg IV, in 30 minutes.

	Cmax (mg/l)	AUC_{0-last} (mg-h/L)	t½ (h)	V_{SS} (L)	CL_T (L/h)	CL_R (L/h)	U (%)
Normal CrCl>80 ml/min	20.6 ± 2.0	52.4 ± 6.9	3.4 ± 0.3	15.8 ± 1.8	4.8 ± 0.6	4.3 ± 0.5	91.6 ± 6.5
Mild (CrCl 50-80 ml/min)	20.1 ± 1.4	72.7 ± 13.9	4.7 ± 0.8	18 ± 0.7	3.4 ± 0.7	2.4 ± 0.6	71.1 ± 7.3
Moderate (CrCl 30-50 ml/min)	24.4 ± 1.65	139 ± 15.7	6.8 ± 1.1	14.2 ± 0.8	1.6 ± 0.2	0.8 ± 0.2	51.9 ± 9.9
Severe (CrCl <30 ml/min)	22.8 ± 3.4	174 ± 44.5	11.1 ± 1.9	16.9 ± 2.39	1.2 ± 0.3	0.4 ± 0.2	31.5 ± 9.6

Dialysis. Dose: 250 mg IV, in 120 minutes.

	Cmax (mg/l)	AUC_{0-last} (mg-h/L)	t½ (h)	V_{SS} (L)	CL_T (L/h)	CL_R (L/h)	U (%)
Healthy subjects	11.1 ± 1.7	44.3 ± 7.1	3.0 ± 0.4	24.4 ± 3.6	5.6 ± 0.7	5.1 ± 0.8	88.6 ± 4.06
Pre-dialysis	13.3 ± 2.3	118 ± 8.73	20.7 ± 1.83	52.5 ± 5.2	1.7 ± 0.10	N/A	N/A
Post-dialysis	21.1 ± 14.7	249 ± 49.0	20.5 ± 5.33	23.9 ± 5.1	0.8 ± 0.2	N/A	N/A

Cmax: maximum plasma concentration; AUC_{0-last}: area under the curve between zero and last plasma concentration; t½: excretion half-life; V_{ss}: volume of distribution in state of equilibrium; Cl_r: kidney clearance; Cl_t: total clearance; U: percentage of drug actively excreted by urine.

dialysis session is 68% and average dialysis clearance is 7.91 l/h [16].

A population pharmacokinetic (PK) study assessing the need for dose adjustment, demonstrated that kidney function expressed in the form of creatinine clearance was the only patient characteristic s with impact on ceftobiprole PK [17].

These data justify use of conventional doses in patients who present with mild kidney failure (CrCl between 50 and 80 ml/min), but recommending the administration of 500 mg every 12 hours via intravenous perfusion for a period of 2 hours when kidney failure is moderate (CrCl 30 - <50 ml/min), and reducing the dose 250 mg administered every 12 hours for a period of 2 h for patients with severe kidney failure (CrCl <30 ml/min). In the event that intermittent dialysis is needed, the recommended dose is 250 mg administered once every 24 hours [5].

Critically ill patients. The impact on the pharmacokinetic parameters of ceftobiprole on the presence of hyperdynamic circulation characterised by elevated creatinine clearance, typical of some critically ill patients, has been assessed in a multicenter, open-label, parallel-group, non-randomized study [18]. Thirty-three adult subjects hospitalised in the Intensive Care Unit were evaluated, who received 1000 mg of ceftobiprole as a 4-h perfusion. Systemic clearance of ceftobiprole was significantly higher in patients with creatinine clearance above 150 ml/min compared to those with normal clearance or reduced creatinine clearance (table 3).

In patients which presented elevated creatinine clearance the drug is excreted from the plasma faster but at the same time there is greater distribution, preventing changes to the excretion half-life but leading to lower plasma concentrations. The authors indicated that ceftobiprole administered in a 4-hour infusion time was able to reach and maintain a plasma concentration of the free drug that exceeded MIC throughout the dosing interval. At a dose of 500 mg, the T>MIC value was 91%, demonstrating that the conventional dose administered in a 4-h infusion also provided therapeutic concentrations [18].

Therefore, prolonging the infusion to 4 hours may optimise drug exposure with a standard dose of ceftobiprole of 500 mg/8 h administered to patients with creatinine clearance above 150 ml/min [5].

Paediatric patients. The pharmacokinetic properties of ceftobiprole have been evaluated in 55 children aged 3 months to 18 years requiring systemic antibiotic therapy [19]. The drug was administered in a 2-hour infusion with doses adjusted to 15 mg/kg for patients aged 3 months to 6 years, 10 mg/kg when aged 6 to 12 years, and 7 mg/kg in patients aged 12 to 18 years. Ceftobiprole exposure, expressed in Cmax and $AUC_{0-\infty}$, was 20% and 40% below that of adults for patients under 12

Table 3 **Ceftobiprole. Pharmacokinetic parameters (mean ± standard deviation) in patients with elevated creatinine clearance (CrCl) [18]**

	Cmax (mg/l)	AUC_{0-last} (mg-h/L)	t½ (h)	V_{SS} (L)	CL_T (L/h)	F (%)
Reduced[a] CrCl 50-79 ml/min (N=5)	51.6 ± 11.2	405 ± 93.2	4.5 ± 1.0	23.7 ± 6.6	3.8 ± 0.6	19.1 ± 4.4
Normal[b] CrCl 80-150 ml/min (N= 20)	37.8 ± 7.3	269 ± 116	3.8 ± 1.6	23.1 ± 6.3	5.2 ± 1.2	20.5 ± 7.3
Elevated[b] CrCl >150 ml/min. (N= 6)	27.6 ± 7.3	180 ± 75.3	3.8 ± 1.2	29.4 ± 7.5	7.4 ± 1.5	21.6 ± 3.5

N: number of subjects. Cmax: maximum plasma concentration; AUC_{0-last}: area under the curve between zero and last plasma concentration; t½: excretion half-life; V_{ss}: volume of distribution at steady state; Cl_t: total clearance; F: percentage of binding to plasma proteins.

[a]Ceftobiprole 1000 mg administered in 4 h. of infusion every 12 h.

[b]Ceftobiprole 1000 mg administered in 4 h. of infusion every 8 h.

years old and those aged 12-18 years, respectively. When the dose was adjusted by body weight, the volume of distribution and total clearance decreased in relation to increased age, while kidney clearance and excretion half-life remained unchanged. The lowest detected exposure in children aged 12 to 18 years should be considered when establishing the most appropriate dosing regimen. However, in this age sub-group, in the PK/PD study, the ceftobiprole concentration remained higher than the MIC of 4 mg/l for 66.5-75.3% of the 8-hour dosing interval and the drug was also well tolerated [19].

Obese patients. A pharmacokinetic study was conducted in 13 morbidly obese adult patients (BMI >40 kg/m^2) administered a single 500-mg dose of ceftobiprole in 2-hours and compared to PK in subjects who were not obese [20]. A lower Cmax was reported in obese patients (21.4 ± 3.0 versus 30.2 ± 4.3 mg/l), lower $AUC_{0-\infty}$ (91.0 ± 11.7 vs. 110 ± 20.1 mg h/l), higher volume of distribution (27.2 ± 3.9 vs. 21.6 ± 5.1 l), and higher total clearance (5.6 ± 0.7 vs. 4.7 ± 0.7), although with similar half-life values (3.4 ± 0.3 vs. 3.2 ± 0.5). Despite these changes in pharmacokinetic parameters, the plasma concentration of ceftobiprole not bound to proteins remained above an MIC of 4 mg/l for 76.6 and 79.7% of the 8-hour interval, respectively, for both obese and non-obese subjects. Therefore, although in obese subjects the volume of distribution and clearance are greater and the AUC lower, the therapeutic objective is reached in a manner similar with the conventional dose, thus a dose adjustment is not needed in this type of patient.

Other situations

Other external clearance techniques. No studies have reported on the effect of different external clearance techniques, hemofiltration, etc. on the pharmacokinetic behaviour of ceftobiprole. However, it should be considered that it has a molecular weight of 534.56 g/mol, binds to proteins in lower proportion (<20%) and its volume of distribution indicates that the drug remains in accessible areas, characteristics which require one to consider the necessity of using higher than recommended doses according to the patient's kidney function, without a specific amount being needed.

Liver failure. The pharmacokinetics of ceftobiprole in patients with liver failure has not been established. Since ceftobiprole endures minimal liver metabolism and is essentially excreted unaltered in the urine, liver failure is not expected to affect ceftobiprole clearance.

Elderly patients. Population Pharmacokinetic data has demonstrated that age as an independent parameter has no effect on the pharmacokinetics of ceftobiprole. Dose adjustment is not believed to be required in elderly patients with normal kidney function.

Gender. Systemic exposure to ceftobiprole was higher in women than in men; 21% for Cmax and 15% for AUC in one study, and 32% and 21%, respectively, in another study. However, the parameter of % T > MIC was similar in both sexes. Therefore, dose adjustment is not believed to be necessary based on gender [16].

Race. Pharmacokinetic population assays (including groups of Caucasians, black patients, and others) and a specific pharmacokinetics study on healthy Japanese subjects showed that race had no effect on the pharmacokinetics of ceftobiprole. Therefore, dose adjustment is not believed to be necessary based on race [16].

PHARMACOKINETICS/PHARMACODYNAMICS

For beta-lactam antibiotics, the concentration exposure time above the MIC value (T>MIC) is the pharmacokinetic/pharmacodynamic index (PK/PD) shown to be most related to therapeutic efficacy [21], hence it is the parameter evaluated when establishing the dose to be used for a drug in this group [22-23].

Studies conducted on laboratory animals have demonstrated an important relationship between the efficacy of ceftobiprole and the T > MIC value. Ceftobiprole demonstrated time-dependent killing; its in vivo postantibiotic effects varied from 3.8 h to 4.8 h for MRSA and from 0 to 0.8 h for penicillin-resistant *Streptococcus pneumoniae*, a bacteriostatic effect was already associated with a T > MIC value of 36-45% in the case of *Enterobacteriaceae,* 14–28% for *S. aureus* and 15–22% for *S. pneumoniae*. In this study, the T > MIC for the 2-log kill dose for strains of *Enterobacteriaceae* (64.5% ± 25.1% of the dosing interval) was also significantly longer than those for the strains of *S. pneumoniae* and *S. aureus* (25.8% ± 4.8% and 29.3% ± 4.6%, respectively) [24].

Based on the findings of *in vivo* models for mice with pneumonia and mouse thigh infection, the doses that produced a T > MIC of 30% were selected for documented gram positive bacteria and 50% in the case of infections due to mixed flora, Gram-positive bacteria, and Gram-negative bacteria. A T> MIC of 50% was used to determine the PK/PD breakpoint of 4 mg/l (EUCAST), with which it is expected to reduce 1-2 $\log_{10}$ the number of bacterial colony-forming units (CFU) [4, 25, 26].

In another study, the activity of ceftobiprole on mice with pneumonia caused by *S. aureus* was explored, demonstrating that T > MIC of ceftobiprole on BAL to cause a reduction in colony-forming units of 1 and 2 $\log_{10}$, was 13 and 24%, respectively. Based on a Monte Carlo simulation and using the concentrations described for the administration of 500 mg/8 h ceftobiprole in a 2-h infusion, and the distribution of MICs from 4950 strains of methicillin-resistant *S. aureus,* an accumulated response fraction of 85.6% was expected to reduce by 1 $\log_{10}$ the number of CFU/g and 79.7% to reduce bacterial load by 2 $\log_{10}$ [12].

In a Monte Carlo simulation conducted with the data collected during phase I trials using pharmacokinetic population models [27], different dosing regimens of ceftobiprole were studied to reach a therapeutic target of T > MIC of 30-60% for MIC values of 1-16 mg/l. Ceftobiprole 500 mg/8 h demonstrated a likelihood to reach a therapeutic target of 100% for T > MIC 30 and 40% and 99% for T > MIC of 50% for an MIC of 4 mg/l and a likelihood of 100% for T > CMI of 50-60% for an MIC of 2 mg/l [25].

In another Monte Carlo simulation performed using pharmacokinetic data from 150 subjects enrolled in phase I and phase II studies, the probability of target attainment (PTA) for ceftobiprole 500 mg/8 h, administered over 30 minutes, 1 or 2 h of infusion, was determined to achieve T > MIC values of 30-60% with different MICs (0.25–8 mg/l). The likelihood of reaching T > MIC of 40-60% with the proposed dosing regimen was greater than 90% for MICs of 3 to 4 mg/l [28].

Considering all reported results, the Monte Carlo simulations, and some other publications [29-31], the dose of 500 mg infused in 2 h., administered every 8 h, is optimal for achieving the proposed T> MIC values when the MIC is ≤4 mg/l; that is, at the non-species-specific sensitivity breakpoint.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest in the creation of this article.

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