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 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.
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 days was determined [7]. In adult patients who received 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-∞}) 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

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### Table 1

| Dose (mg) | Perfusion time (hours) | Cmax (mg/l) | AUC_{0-∞} (mg h/l) | t½ (h) | Vd (l) | Plasma protein binding (%) | Cl (l/h) | Active urinary excretion (%) |
|-----------|------------------------|-------------|-------------------|--------|-------|---------------------------|----------|---------------------------|
| 500       | 2                      | 29.2 ± 5.5  | 104 ± 13          | 3.1 ± 0.3 | 21.2 ± 3.3 | 16                         | 4.8 ± 0.7 | 83.1 ± 9.1                |

Cl: total clearance

Vd: volume of distribution

t½: elimination half-life

AUC_{0-∞}: extrapolated area under the curve

Cmax: maximum plasma concentration

Vd: volume of distribution

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].

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 load to below detectable limits in all animals treated, while it was reduced by 73% in animals treated with vancomycin or linezolid [11].
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 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].

**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<sub>0-last</sub> (mg-h/L) | t½ (h) | V<sub>SS</sub> (L) | Cl<sub>T</sub> (L/h) | Cl<sub>R</sub> (L/h) | U (%) |
|---|---|---|---|---|---|---|---|
| Normal | 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<sub>0-last</sub> (mg-h/L) | t½ (h) | V<sub>SS</sub> (L) | Cl<sub>T</sub> (L/h) | Cl<sub>R</sub> (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<sub>0-last</sub>: area under the curve between zero and last plasma concentration; t½: excretion half-life; V<sub>SS</sub>: volume of distribution in state of equilibrium; Cl<sub>T</sub>: kidney clearance; Cl<sub>R</sub>: total clearance; U: percentage of drug actively excreted by urine.
Ceftobiprole: pharmacokinetics and PK/PD profile

J. R. Azanza Perea, et al.
Rev Esp Quimioter 2019;32 (Suppl. 3): 11-16

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

Based on the findings of $\text{in vivo}$ models for mice with pneumonia and mouse thigh infection, the doses that produced a $T > \text{MIC}$ 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 $T > \text{MIC}$ of $50\%$ was used to determine the $\text{PK/PD}$ breakpoint of $4 \text{ mg/l (EUCAST)}$, 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 $T > \text{MIC}$ 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 $500 \text{ mg/8 h}$ ceftobiprole in a $2\text{-h}$ 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 $T > \text{MIC}$ of $30-60\%$ for MIC values of $1-16 \text{ mg/l}$. Cefotobiprole $500 \text{ mg/8 h}$ demonstrated a likelihood to reach a therapeutic target of $100\%$ for $T > \text{MIC}$ 30 and $40\%$ and $99\%$ for $T > \text{MIC}$ of $50\%$ for an MIC of $4 \text{ mg/l}$ and a likelihood of $100\%$ for $T > \text{CMi}$ of $50-60\%$ for an MIC of $2 \text{ mg/l}$ [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 $500 \text{ mg/8 h}$, administered over $30$ minutes, $1$ or $2\text{ h}$ of infusion, was determined to achieve $T > \text{MIC}$ values of $30-60\%$ with different MICs (0.25–8 mg/l). The likelihood of reaching $T > \text{MIC}$ of 40–60% with the proposed dosing regimen was greater than $90\%$ for MICs of $3$ to $4 \text{ mg/l}$ [28].

Considering all reported results, the Monte Carlo simulations, and some other publications [29–31], the dose of $500 \text{ mg}$ infused in $2\text{ h}$, administered every $8\text{ h}$, is optimal for achieving the proposed $T > \text{MIC}$ values when the MIC is $\leq 4 \text{ mg/l}$; 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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