Ceftobiprole review

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ABSTRACT

Ceftobiprole is a fifth generation cephalosporin with a series of characteristics differentiating it from other beta-lactams, including its antibacterial activity, mainly against methicillin-resistant Staphylococcus aureus, resistant Streptococcus pneumoniae and also Gram-negative microorganisms such as Pseudomonas aeruginosa. This antibiotic has been subjected to various clinical trials and the results of these have led to its approval in Spain for the treatment of nosocomial pneumonia, excluding that associated with mechanical ventilation, and community-acquired pneumonia. The results of various ceftobiprole clinical studies provide consistent information on efficacy and tolerability. Ceftobiprole as monotherapy has been shown to be non-inferior to comparator antibiotics in different settings. Information is available on its compatibility with other drugs in Y-site administration, important from the point of view of the intravenous treatment of patients who present venous access limitation. On the other hand, and in contrast to other cephalosporins, ceftobiprole presents a low risk of infection due to Clostridium difficile and, in comparison with ceftaroline, neutropenia has not been reported to present any significant issues.

Keywords: ceftobiprole, tolerability, safety, Y-site administration

INTRODUCTION

Ceftobiprole is a cephalosporin that has as a number of differences compared to most other compounds of this family of beta-lactams, its activity against methicillin-resistant Staphylococcus aureus (MRSA) and Streptococcus pneumoniae resistant to third-generation cephalosporins and penicillin [1]. Ceftobiprole is excreted mainly in the urine in an unaltered form and with a high recovery of the administered dose of the drug [2]. The information from the clinical trials evaluating the pharmacokinetics of ceftobiprole shows that the AUC and $C_{\text{max}}$ values are proportional to the doses that were used. Likewise, using data from the participants in these trials the degree of dose modification required based on alterations in renal function has been established (table 1) [3]. In the following, we describe the tolerability and safety of ceftobiprole.

| Table 1 | Ceftobiprole dose adjustment according to renal function* |
|---------|-----------------------------------------------------------|
| Normal renal function | 500 mg/8h |
| CrCl 50-80 mL/min | 500 mg/8h |
| CrCl 30-49 mL/min | 500 mg/12h |
| CrCl < 30 mL/min | 250 mg/12h |

*The proposed adjustment is based on the Cockcroft-Gault formula and a standard dose of 500 mg / 8h intravenously. The dose is based on a 2-hour infusion.

SAFETY AND TOLERABILITY OF CEFTOBIPROLE IN CLINICAL TRIALS

A phase I study in which a single dose ranging from 125 mg to 1,000 mg was administered aimed at analysing the pharmacokinetics and safety of ceftobiprole. One study objective was to establish the duration of time with ceftobiprole concentration maintained above the MIC, since, as a beta-lactam antibiotic, its efficacy is related to the pharmacokinetic-pharmacodynamic index of $T > \text{MIC}$ [4]. The safety of the drug was assessed in 40 patients, eight (20%) of whose presented a total of 10 adverse effects. Only 3 adverse events of moderate importance were recorded (nausea and vomiting), with taste changes...
observed in the remaining 7 cases. No serious adverse effects were detected. When the study was extended to multiple doses in 16 healthy male volunteers, 5 patients had at least one adverse effect in the 500 mg group versus 6 in the 750 mg group compared to 3 in the placebo group. The number of adverse events was higher in patients receiving the highest dose, with a total of 22 mild and 5 moderate events, and reversible taste alteration again predominating [5]. A network meta-analysis compared the efficacy and safety of ceftobiprole versus 8 other antibiotics for the treatment of Hospital-acquired pneumonia [6]. The results showed no significant differences in the adverse effects of this cephalosporin against the rest of the comparator agents. A double-blind, randomized, multinational clinical trial compared the efficacy and safety of ceftobiprole versus vancomycin in the treatment of skin and soft tissue infections caused by gram-positive organisms [7]. A total of 784 patients were included in the study. Adverse effects and concomitant diseases were the main reasons for patient discontinuation in the study. A total of 52% of the patients presented at least one adverse event in the ceftobiprole group compared to 51% in the vancomycin group. Serious side effects were observed in 6% of patients in each group, 4% and 6% of patients discontinued the study drug in the ceftobiprole and the vancomycin group, respectively. Nausea and vomiting were the most frequent adverse effects, reaching 21% in the ceftobiprole group versus 12% in the vancomycin group. In the vancomycin group 3 deaths were recorded compared to none in the ceftobiprole group. None of the deaths were attributed to antibiotic treatment. Similar results were observed in another phase III clinical trial in this same indication with 56% patients presenting adverse events in the ceftobiprole arm compared to 57% in the comparator group, which in this case was the combination of vancomycin associated with ceftazidime. Four percent of patients discontinued treatment in both groups [8].

One study evaluated the efficacy and safety of ceftobiprole vs ceftriaxone with or without linezolid in patients with community-acquired pneumonia who required hospital admission [9].

A total of 638 patients were included in the analysis. A total of 6% patients discontinued the treatment early in the ceftobiprole group compared to 4% in the comparator group. The incidence of adverse events was 36% in the ceftobiprole group versus 26% with the comparator, the differences being mainly due to the occurrence of nausea and vomiting.

A phase III study analyzed the efficacy of ceftobiprole versus ceftazidime with or without linezolid in the treatment of nosocomial pneumonia, including pneumonia associated with mechanical ventilation (VAP) [10]. A total of 781 patients were randomized, 176 of whom had VAP. A total of 24.9% patients presented some adverse events in the ceftobiprole group compared to 25.4% in the comparator group. Patients in the ceftobiprole group had a lower incidence of diarrhea than those in the ceftazidime plus linezolid group, 3.1% versus 6.5%, respectively. A total of 4.4% patients in the ceftobiprole arm versus 2.6% of patients treated in the comparator group (ceftazidime plus linezolid) developed hyponatremia. Dysgeusia was only observed in the ceftobiprole group, in 1.3% of patients. There were 15 cases of serious adverse events, 3.9% in the ceftobiprole group compared to 3.1% in the comparator.

SAFETY AND TOLERABILITY OF CEFTOBIPROLE IN OTHER STUDIES

One study was conducted to analyse possible modifications of the intestinal microflora produced by the 7-day exposure to treatment with ceftobiprole [11]. A total of 12 healthy volunteers of both genders were included. No fecal excretion of ceftobiprole was observed and only a minimal effect on the fecal flora was reported. Unlike other cephalosporins, ceftobiprole is considered an antibiotic associated with a lower risk of *Clostridium difficile* infection. In a subsequent study in mice, it has been proposed that ceftobiprole has an inhibitory effect on *C. difficile* activity and a moderate effect on the anaerobic microflora [12].

Agranulocytosis associated with prolonged treatment with ceftobiprole, related to a mechanism related to T-cells has been described [13].

Although the understanding of the impact of the inoculum effect in cephalosporins observed *in vitro* is limited, in a study conducted on strains of methicillin-susceptible *S. aureus*, ceftobiprole had the lowest MICs at a high inoculum when compared to other cephalosporins [14]. The significance of these results should be considered alongside the findings of subsequent *in vivo* studies.

A review of the literature analysing the neurological effects attributable to treatment with beta-lactams has been published [15]. This review highlighted renal failure as the main risk factor for production of neurological adverse effects attributable to beta-lactams. Unlike what was observed with other cephalosporins, no case of neurological alterations related to ceftobiprole could be identified in that review.

A case report of combination therapy with daptomycin and ceftobiprole in the treatment of a methicillin-resistant *S. aureus* endocarditis in prosthetic valve has been described [16]. The patient was treated with a dose of 500 mg/8h of ceftobiprole for 11 weeks, with resulting good antibiotic tolerability.

COMPATIBILITY OF CEFTOBIPROLE IN Y-SITE ADMINISTRATION

Patients who require treatment with more than one drug administered intravenously, and have limited venous access, have a higher risk of receiving ineffective treatment when one drug is administered simultaneously with another in Y-site administration [17]. One study aimed to analyze the compatibility of ceftobiprole with other drugs, through visual observation, measurement of turbidity and the appearance of possible particles as a result of Y-site administration. The initial solution of ceftobiprole was diluted as per the product specifications resulted in a turbid-free mixture, without particles. Table 2 shows the compatibility of ceftobiprole with other antimicrobials included in the study.
Table 2

| Antimicrobial           | Concentration (mg/mL) |
|-------------------------|-----------------------|
| Acyclovir               | 7                     |
| Azithromycin            | 2                     |
| Clindamycin phosphate   | 10                    |
| Fluconazole             | 2                     |
| Metronidazole           | 5                     |
| Trimethoprim/sulfamethoxazole | 0.8/4               |
| Voriconazole            | 4                     |

*The information contained in this table is only valid for the specific brands used in the referenced study [16] and at the concentrations indicated.

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