

Fifth Generation Cephalosporins : Drugs To Overcome Antibiotic Resistance

Nisha A. R.¹, Vanishree H.² and Mahesh D. M.²

¹Assistant Professor, ²MVSc Scholars

Department of Veterinary Pharmacology and Toxicology, College of Veterinary and Animal sciences, Pookode, Wayanad, Kerala, India

ABSTRACT

The cephalosporin group of antimicrobials is known for its broad spectrum of activity, proven efficacy and favourable safety profile, making it the most commonly prescribed class of antimicrobials (Bassetti *et al*, 2013) .They are a class of beta lactam antibiotics which are structurally and functionally related to penicillins. Cephalosporins are obtained semisynthetically from a fungus *cephalosporium*. Fifth generation cephalosporins are recently introduced subclass of cephalosporin although the term fifth generation is not universally accepted. The fifth generation cephalosporins are reported to have powerful antipseudomonal characteristics and are less susceptible to development of resistance (Gallagher and Conan, 2013)

Keywords : Cephalosporium, VAP, HAP, QIDP, FDA, CABP, ABSSI, MRSA, MSSA, ESBL, ABSSSI, CABP

I. INTRODUCTION

There are four recognized class generations of cephalosporins based on spectra of activity. First-generation cephalosporins are active against Gram-positive cocci; second generation agents retain this Gram-positive activity and have increased activity against Gram-negative organisms (Roger, 2002). Third generation cephalosporins have decreased activity against Gram-positive organisms relative to first and second generation agents, but improved Gram-negative coverage. Spectrum of activity is further expanded in the fourth-generation agents, which have increased activity against Gram-negative organisms compared with first and second generation agents and greater coverage of gram-positive organisms than third generation agents, as well as activity against *Pseudomonas* spp. and some Enterobacteriaceae, including those that produce β -lactamases (Wlaker,1999). Fifth generation cephalosporins mainly include two drugs .They are Ceftaboprole and Ceftarolone

II. METHODS AND MATERIAL

Ceftaboprolone

Ceftobprole, a new 5th generation cephalosporine for the treatment of hospital-acquired pneumonia (HAP), exventilator associated pneumonia (VAP) and community-acquired pneumonia (CAP) (Bassetti *et al*, 2013). Ceftobiprole is the active moiety of the prodrug ceftobiprole medocaril. The drug received qualified infectious disease product (QIDP) designated from US food and drug administration (FDA) for potential treatment of community acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infection (ABSSI) (Bush,K.,2007) . In India incidence of methicillin resistant staphylococcus aureus is also increasing, 32% of Staphylococcus aureus isolates were found to be multiply, with the individual figures for resistance being 20% (Bombay), 42.5% (Delhi) and 47%(Bangalore) (Mehta, A. A, 1996).

Spectrum of Action

Ceftobiprole has shown in vitro antimicrobial activity against a broad range of Gram-positive and Gram-negative pathogens (Noel, G. J, 2007). Among the Gram-positive pathogens, ceftobiprole has demonstrated good in vitro activity against methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-susceptible *Staphylococcus aureus* (MSSA) and coagulase-negative staphylococci as well as against MRSA strains with reduced susceptibility to linezolid, daptomycin or vancomycin (Von Nussbaum, 2006). Ceftobiprole has also displayed potent activity against *Streptococcus pneumoniae* (including penicillin-sensitive, penicillin-resistant and ceftriaxone-resistant strains) and *Enterococcus faecalis*, but not against *Enterococcus faecium* (El Solh, 2006). For Gram-negative pathogens, ceftobiprole has shown good in vitro activity against *Haemophilus influenzae* (including both ampicillin-susceptible and ampicillin-non-susceptible isolates), *Pseudomonas aeruginosa* and strains of *Escherichia coli*, *Klebsiella pneumoniae* and *Proteus mirabilis* not producing extended-spectrum β -lactamase (ESBL). Like all other cephalosporines, ceftobiprole was inactive against ESBL producing strains (Jones, 2007).

Mechanism of Action

Like other cephalosporins, ceftobiprole exerts its antibacterial activity by binding to important penicillin-binding proteins and inhibiting their transpeptidase activity which is essential for the synthesis of bacterial cell walls by inhibiting transpeptidation and formation of the bacterial cell wall, leading to cell lysis and death (Pratt, R. F, 2008). The drug can bind to several different penicillin binding proteins (PBPs) found in both gram-negative and gram-positive bacteria. Ceftobiprole rapidly binds and forms a stable inhibitory acyl-enzyme complex with PBP 2' (PBP 2a) and PBP 2x, which provide activity against beta-lactam resistant staphylococci and streptococci respectively. The stability of the acyl-enzyme complex, in combination with the long side chain that sits deep in the PBP 2'-binding pocket, enhances the stability of the bond and inhibition of the enzyme.

Pharmacokinetics

Ceftobiprole shows linear pharmacokinetics after single and multiple dosages. Ceftobiprole medocaril is a water-soluble prodrug developed to facilitate the intravenous (IV) administration of the active parent drug, ceftobiprole. As a result of its limited oral bioavailability; it will likely be available in an IV formulation only. Volume of distribution is apparently equal to extracellular fluid. Plasma protein binding is 22% and is excreted by glomerular filtration. Half-life is approximately 3 to 4 hours. Approximately 89% of drug being eliminated as prodrug, open drug and active ring metabolite.

Drug Interactions

Drug interactions are low because of its favourable pharmacokinetic properties. Co administration of warfarin with ceftobiprole sometimes causes an increased prothrombin time and an International Normalized Ratio (INR) (Walsh, 2006). One of the clinically important medications found to be incompatible with ceftobiprole include aminoglycosides, amiodarone (Cordarone), calcium gluconate, diltiazem (Cardizem), dopamine, dobutamine, fluoroquinolones, human regular insulin, hydromorphone, labetalol (Normodyne, Trandate), magnesium sulfate, midazolam (Versed), morphine sulfate, and potassium phosphate. The timing of administration and availability of IV lines are expected to be a concern for patients receiving ceftobiprole with incompatible medications (Rizwi et al, 2011).

Dosage

Based on pharmacokinetic, pharmacodynamic and clinical data published, ceftobiprole dosing is likely to be based on the indication and the intended bacterial coverage (Gould et al, 2011). For cSSSI's caused by culture-proven or presumed gram positive infection, the dose of ceftobiprole is expected to be 500 mg every 12 hours infused over 1 hour (Rizwi et al, 2011). For cSSSIs (including diabetic foot infections) caused by culture-proven or presumed Gram negative or mixed infections, the predicted dosing for ceftobiprole is expected to be 500 mg every 8 hours, infused over 2 hours. Dose adjustment is required in patients with renal insufficiency. Preliminary data suggest that for patients with mild renal impairment (creatinine clearance (CrCl)

of 50-80 ml/min), no dosage adjustment is necessary. In patients with moderate renal impairment the predicted dosing of ceftobiprole would be 500 mg every 12 hours (Anderson et al, 2011).

Ceftarolone

Ceftaroline fosamil, the prodrug of the active metabolite, ceftaroline, is a new, broad-spectrum cephalosporin recently approved in the USA for the treatment of acute bacterial skin and skin structure infections (ABSSSIs) and community-acquired bacterial pneumonia (Ludano et al, 2011). Ceftaroline has potent in vitro activity against Gram-positive organisms and as well as common Gram-negative organisms. The high affinity of ceftaroline for penicillin-binding proteins is responsible for the potent activity observed against clinically relevant pathogens. With respect to the treatment of CABP, the activity of ceftaroline against pathogens such as *S.pneumoniae*, *S. aureus*, *Haemophilus influenzae* and *Moraxella catarrhalis* demonstrates coverage across a broad range of pathogens typically encountered in clinical practice. Ceftaroline is also very active against common pathogens seen in ABSSSIs such as *S. aureus* (methicillin-susceptible *S.aureus* and methicillin-resistant *S.aureus*) and *Streptococcus pyogenes* (Ludano et al, 2011).

Mechanism of Action

Ceftaroline was developed by modifying the structure of the fourth-generation cephalosporin cefozopran (Ge et al 2008). The prodrug, ceftaroline fosamil, which contains a phosphono group to increase water solubility, is rapidly converted in plasma into the bioactive agent, ceftaroline. The 1, 3-thiazole ring attached to the 3-position of the cephalosporin nucleus and the oxime group in the C7 acyl moiety are responsible for the enhanced anti-MRSA activity observed with ceftaroline (Kanafani et al, 2011).

Structure

Like other β -lactams, ceftaroline exerts its rapid bactericidal effect by binding to key penicillin-binding proteins (PBPs). Methicillin resistance is associated with PBP 2A, for which most β -lactams have low affinity. Competition assay studies have demonstrated that ceftaroline has a high affinity for staphylococcal PBPs 1, 2 and 3, and for MRSA PBP 2A (Biek, 2010).

Spectrum of Activity

Ceftaroline has a broad-spectrum of activity against Gram-positive and Gram-negative organisms. Gram positive organisms include *Staphylococcus aureus* (MRSA, MSSA), coagulase negative staphylococci, *Enterococcus faecalis*, *Listeria monocytogenes*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes* (macrolide resistant and macrolide susceptible), β -Haemolytic group A streptococci and β -Haemolytic group B streptococci.

Gram negative organisms include *Enterobacter cloacae*, *Haemophilus influenzae*, *E.coli*, *Shigella* spp, *Klebsiella pneumoniae*, *Pasteurella multocida* and *Klebsiella oxytoca* (Biek,2010).

III. RESULTS AND DISCUSSION

Drug Interactions

No clinical drug–drug interaction studies have been conducted with ceftaroline fosamil. There were no clinically relevant differences in ceftaroline exposure included in the skin and pneumonia trials who were taking concomitant medications known to be inducers, inhibitors or substrates for cytochrome P450 isozymes or drugs that undergo active renal secretion or drugs that modify renal blood flow (Steed et al, 2010). When ceftaroline was incubated in vitro with pooled human liver microsomes, it did not induce or inhibit P450 isozymes. Available data suggest that ceftaroline fosamil has a low propensity for drug interaction (Ludano et al, 2011).

Dosing and Administration

Ceftaroline fosamil is dosed at 600 mg IV every 12 h over 1 h in adults ≥ 18 years of age. Dosage adjustment is necessary in patients with moderate to severe renal impairment. In patients with moderate renal impairment (CLCR .30 –50 mL/min), the dosage should be reduced to 400 mg IV (over 1 h) every 12 h (Corey, et al, 2010). Patients suffering from severe renal impairment (CLCR 15 – 30 mL/min) should have the dose reduced to 300 mg IV (over 1 h) every 12 h (Lichtman, 2007). For patients with end-stage renal disease, including those on haemodialysis, the dose should be further reduced to 200 mg IV every 12 hours. Ceftaroline fosamil is

available in 600 mg and 400 mg single use vials of sterile powder. The vial contents should be reconstituted with 20 mL of sterile water and further diluted in 250 mL of normal saline, 5% dextrose solution, 2.5% dextrose and 0.45% sodium chloride solution, or Lactated Ringer's Injection (Jorgenson, 2011). The resulting solution should be used within 6 h if stored at room temperature or within 24 h if refrigerated. Systemic exposure following intramuscular administration of 600 mg of ceftaroline fosamil to healthy adults was equivalent to systemic exposure following IV administration (Van Wart, 2013).

IV. CONCLUSION

Ceftaboprole and Ceftarolone can be used to reduce the development of drug-resistant bacteria and maintain the effectiveness other antibacterial drugs. But these drugs should be used to treat only ABSSSI or CABP that are proven or strongly suspected to be caused by susceptible bacteria. Before administration of both of these drugs appropriate specimens for microbiological examination should be obtained and causative organisms should be isolated. If the causative organisms are not isolated and identified, local epidemiology and susceptibility patterns can contribute to the empiric selection of therapeutic agent.

V. REFERENCES

- [1]. Anderson, S. D and John G. G. Ceftobiprole: an extended-spectrum anti-methicillin-resistant *Staphylococcus aureus* cephalosporin. *Annals of Pharmacotherapy* 42.6 (2008): 806-816.
- [2]. Bassetti, Matteo, New antibiotics for bad bugs: where are we? *Annals of clinical microbiology and antimicrobials* 12.1 (2013): 1.
- [3]. Biek, D. Ceftaroline fosamil: a novel broad-spectrum cephalosporin with expanded anti-Gram-positive activity. *Journal of antimicrobial chemotherapy*. 65.suppl 4 (2010): iv9-iv16.
- [4]. Bush, K. Anti-MRSA β -lactams in development, with a focus on ceftobiprole: the first anti-MRSA β -lactam to demonstrate clinical efficacy. *Expert opinion on investigational drugs* 16.4 (2007): 419-429.
- [5]. Corey, G. R. Canvas 1: the first Phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. *Journal of antimicrobial chemotherapy* 65.suppl 4 (2010): iv41-iv51.
- [6]. El Solh, Ali. A. Ceftobiprole: a new broad spectrum cephalosporin. *Expert opinion on pharmacotherapy* 10.10 (2009): 1675-1686.
- [7]. Gallagher, J C., and Conan M. *Antibiotics simplified*. Jones & Bartlett Learning, 2013.
- [8]. Ge, Yigong. In vitro profiling of ceftaroline against a collection of recent bacterial clinical isolates from across the United States. *Antimicrobial agents and chemotherapy* .52.9 (2008): 3398-3407.
- [9]. Gould, I. M. Management of serious methicillin-resistant *Staphylococcus aureus* infections: what are the limits? *International journal of antimicrobial agents*. 37.3 (2011): 202-209.
- [10]. Jones, M. E. In-vitro profile of a new β -lactam, ceftobiprole, with activity against methicillin-resistant *Staphylococcus aureus*. *Clinical Microbiology and Infection* 13.s2 (2007): 17-24.
- [11]. Jorgenson, M.R., Daryl D. D, and Peggy L. C. Ceftaroline fosamil: a novel broad-spectrum cephalosporin with activity against methicillin-resistant *Staphylococcus aureus*. *Annals of Pharmacotherapy*. 45.11 (2011): 1384-1398.
- [12]. Kanafani, Z. A and G. Ralph Corey. Ceftaroline: a cephalosporin with expanded Gram-positive activity. (2009): 25-33.
- [13]. Laudano, J. B. "Ceftaroline fosamil: a new broad-spectrum cephalosporin. *Journal of antimicrobial chemotherapy*.66.suppl 3 (2011): iii11-iii18.
- [14]. Lichtman, S. M. International Society of Geriatric Oncology (SIOG) recommendations for the adjustment of dosing in elderly cancer patients with renal insufficiency. *European journal of cancer* 43.1 (2007): 14-34.
- [15]. Mehta, A. A. A pilot programme of MRSA surveillance in India. (MRSA Surveillance Study Group). *Journal of Postgraduate medicine* 42.1 (1996): 1.
- [16]. Noel, G. J. Clinical profile of ceftobiprole, a novel β -lactam antibiotic. *Clinical Microbiology and Infection* .13 (2007): 25-29.
- [17]. Pratt, R. F. Substrate specificity of bacterial DD-peptidases (penicillin-binding proteins). *Cellular and Molecular Life Sciences*. 65.14 (2008): 2138-2155.
- [18]. Rizvi, M. W. Ceftobiprole-A novel cephalosporin to combat MRSA. *Eastern Journal of Medicine* 16.1 (2011): 1.

- [19]. Roger, G. Little II. "Identification of novel antimicrobial agents using metabolic oxidation-reduction indicator dyes." U.S. Patent No. 6,436,660. 20 Aug. 2002.
- [20]. Steed, M. E., and Michael J. R. "Ceftaroline: A New Cephalosporin with Activity against Resistant Gram-Positive Pathogens. "Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy 30.4 (2010): 375-389.
- [21]. Van Wart, S. A., Population pharmacokinetics of ceftaroline in patients with acute bacterial skin and skin structure infections or community-acquired bacterial pneumonia. *The Journal of Clinical Pharmacology* 53.11 (2013): 1155-1167.
- [22]. Von Nussbaum, F. Antibacterial natural products in medicinal chemistry - exodus or revival?" *Angewandte Chemie International Edition*. 45.31 (2006): 5072-5129.
- [23]. Walker, R. C. "The fluoroquinolones." *Mayo Clinic Proceedings*. Vol. 74(10) Elsevier, 1999.
- [24]. Walsh, C. "Molecular mechanisms that confer antibacterial drug resistance." *Nature*. 406.6797 (2000): 775-781.