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A Review on Ceftiofur Sodium

Faiza Hassan[1], Sidra Altaf[2], Misbah Ijaz[3] and Muhammad Tahir Mohy-ud-din [4]

[1,2] Institute of Pharmacy, Phyisology & Pharmacology,
Faculty of Veterinary Science, University of Agriculture,
Faisalabad 38000, Pakistan

[3 , 4] Department of Clinical Medicine & Surgery,
Faculty of Veterinary Science, University of Agriculture
Faisalabad 38000, Pakistan

Abstract

Ceftiofur is third generation cephalosporin, broad spectrum antibiotic. It inhibits the cell wall synthesis of bacteria. Ceftiofur is widely used in animals for the treatment of various diseases. Ceftiofur is used against Gram positive and Gram negative bacteria. It has been approved world widely for the treatment of respiratory diseases in sheep, goats, cattle and horses. Ceftiofur sodium pharmacokinetic alters when it is administered with some other drugs.

Keywords: *Cephalosporins, Broad spectrum, Cell wall synthesis Pharmacokinetics*

1. Introduction

Ceftiofur is the only third-generation cephalosporin approved for use in cattle in the United States and is currently labeled for the treatment of bovine pneumonia, interdigital necrobacillosis, acute metritis and mastitis. Cephalosporins are the group of antibiotics which are routinely used in human and in animals. Cephalosporin is actually semi-synthetic antibiotics which structurally and functionally resemble penicillin. There are four generations of cephalosporins and all possess sub-structure β-lactame, also present in penicillin (Hornish and Kotarski, 2002; Petri, 2011). All members of cephalosporin group have a nucleus, 7 aminocephalosporanic acids. This nucleus comprises of two rings fused with each other viz dihydrothiazine ring and β-lactame ring (Petri, 2011). The members of cephalosporin groups are either used in the form of free base or as sodium salts. Mechanism of action of cephalosporins is attributed to disruption of cell wall synthesis by specific binding to penicillin-binding proteins (PBPs). These proteins are present on bacterial cell surface and involve in synthesis of bacterial cell wall. Cephalosporins target enzymes and inhibit the transpeptidation of peptidoglycane. The β-lactame ring is important for antibacterial activity of cephalosporin (Prescott, 2006).

Ceftiofur has important applications to both human and veterinary medicine due to their broad-spectrum, generally bactericidal effects (Whichard et al., 2005; Tenover, 2006). The Upjohn Company in 1988 introduced the ceftiofur in veterinary medicine as the sodium salt Naxcel®. Then, the hydrochloride salt of ceftiofur Excenel® was introduced which is more stable form. It consists of oxyiminoaminothiazolyl group and, at position 3, contains furoic acid thioester. As ceftiofur molecule has zwitter ionic characteristic, its different salt forms can be synthesized. Ceftiofur exhibits very good activity against a wide range of bacteria i.e. Gram-negative as well as Gram-positive including β-lactamase producing strains. Broad spectrum activity of ceftiofur is due to its important characteristic of being resistant to inactivation by β-lactamase produced by some bacteria. This property of ceftiofur is attributed to the presence of bulky imino-

methoxy side chain (Klein and Cunha, 1995; Dolhan et al 2014). It is bactericidal and like other cephalosporins, it kills the bacteria by disrupting the cell wall synthesis (Prescott, 2006). It has been approved world widely for the treatment of respiratory diseases in sheep, goats, cattle and horses (Hornish and Kotarski, 2002). Ceftiofur is also considered as an effective approach for treating and controlling respiratory distress in horses caused by Streptococcus zooepidemicus (Guglick et al., 1998).

2. Antibacterial Spectrum of Ceftiofur

Ceftiofur has a broad antibacterial spectrum and is effective against both Gram positive and Gram negative bacteria as well as some anaerobic bacteria. It has good efficacy against Escherichia coli, Pasteurella multocida, Actinobacillus pleuropneumoniae, Haemophilus and Salmonella Spp. (Jaglan et al., 1992). Due to its broad spectrum activity, it is also proposed for the treatment of mastitis in animals (Owens et al., 1990). In mice, antibacterial activity of ceftiofur sodium was investigated both under in vitro and in vivo conditions. It was observed that against all tested strains, in which β-lactamase producing organisms were also present, ceftiofur showed better activity than ampicillin. Ceftiofur also showed good antibacterial activity in mice having E.coli induced lethal diarrhea and Staphylococcus aureus induced mastitis (Yancey et al., 1987).

In horses for treatment of respiratory tract infection use of ceftiofur sodium was evaluated. For this study horses having naturally acquired respiratory infection were selected. These horses were given ceftiofur sodium and ampicillin for comparison and to check the efficacy of ceftiofur for respiratory disease treatment. Results showed that ceftiofur sodium therapy for respiratory tract infections in horses is safe and effective. Folz et al., 1992.

The therapeutic efficacy of ceftiofur with high dose for treatment of experimentally induced salmonellosis in new born calves was investigated. Salmonella enteritica serovar Typhimurium was given orally to calves for induction of salmonellosis. Calves were randomly divided in to two groups, medicated and non-medicated. It was observed that treatment with ceftiofur significantly decreased the diarrhea and temperature .Fecal shedding of salmonella was also significantly reduced in treated calves as compared with non-medicated group. It was concluded that ceftiofur use may enhance the clearance of salmonella and also increase animal welfare by reducing fecal shedding of salmonella. (Fecteau et al., 2003).
The effect of therapeutic ceftiofur administration to dairy cattle on Escherichia coli dynamics in the intestinal tract was also examined by testing the ceftiofur-treated and untreated cattle in a normally functioning dairy to examine enteric Escherichia coli for changes in antibiotic resistance profiles and genetic diversity (Singer et al., 2008).

Antibacterial activity of Ceftiofur sodium was evaluated as anti-infective chemotherapeutic agent in birds against different bacterial pathogens. The obtained results showed that it was more effective and superior in its action than that the other compared antibacterial agents. The disc diffusion test discovered that most P. multocida isolates were highly sensitive to ceftiofur sodium .(Al-Kheraije 2013).

3. Drug Interaction of ceftiofur sodium:

Potential pharmacokinetic interactions between ceftiofur sodium and aspirin were evaluated and in addition, in this research the potential for interaction between ceftiofur and its active metabolites and the organic anion transporter was also studied. . The organic anion transporter substrate used in this evaluation was probenecid. 10 healthy non-pregnant, non-lactating dairy cows were used for this purpose. No statistically significant changes were detected as a result of preceding treatment with aspirin. Preceding treatment with probenecid resulted in a decrease in both CI (0.007 f 0.005 L/kg/h) and MRTp (0.89 f 0.45h). These results suggest that ceftiofur or its metabolites may interact with the organic anion transporter, but that consideration of alterations to dose and dose interval may not be necessary when ceftiofur sodium is administered to the cow concomitantly with a single dose of aspirin. (Whittem et al.,1995).
The changes in mandible and serum cephalosporin levels when concurrently administered with ibuprofen in hyperlipidemic rats were determined. There is increase in cephalosporin level in hyperlipidemic as well as in control group when non-steroidal anti-inflammatory drugs (NSAIDs) were administered along with cephalosporin. It was concluded from study that NSAIDs exhibit antagonistic response in binding

of protein which results in higher antibiotic concentration in serum. (Tsivou et al., 2005).
The effect of dipyron on pharmacokinetic of ceftiofur sodium in feverish and healthy cows was investigated when both drugs were co-administered (Tohamy 2008). After single intravenous (i.v) as well as intramuscular (i.m) administration of both drugs concomitantly pharmacokinetic parameters were observed. Higher volume of distribution at steady state (Vd(ss)) and total body clearance (CIB) were observed in feverish cows as compared to healthy animals. In case of intramuscular (i.m) administration of ceftiofur, high peak serum concentration (Cmax) was observed in healthy cows. The obtained results showed that in feverish animals absorption of drug was increased with short absorption half-life.

4. Pharmacokinetics of ceftiofur sodium:

The effect of age on the pharmacokinetics of ceftiofur sodium was studied by Brown et al., 1996. For this purpose two groups were made, group I comprised of sixteen one day old Holstein bull calves and 14 six month old Holstein stear were placed in group II. A dose of 2.2 mg/kg of ceftiofur sodium was evaluated in animals of two different age groups. Blood samples were collected and plasma concentration of ceftiofur was determined as desfuroylceftiofur acetamide (DCA) through HPLC. From the results it was concluded that ceftiofur sodium at approved dose of 1.1-2.2 mg/kg may provide plasma concentration more than MIC for longer period of time in neonates as compared to older calves.

The pharmacokinetics of ceftiofur sodium was determined in different birds after subcutaneous and intramuscular dosing by Tell et al., 1998. The maximum concentration (Cmax) and area under the concentration time curve (AUC) in chicks and poults were dose-proportional. The Cmax for cockatiels was 5.2 µg/mL and for Amazon parrots was 11 µg/mL. Clearance in cockatiels and Amazon parrots were 11.3 and 3.8 mL/min/kg, respectively, and reflected the much greater AUC seen in Amazon parrots. Clearance values of ceftiofur were similar in chicks and Amazon parrots, slightly greater in turkey poults and greatest in cockatiels. These results indicate that pharmacokinetic differences must be considered when establishing dosage regimens for different avian species.

The pharmacokinetics of ceftiofur sodium as well as its bioequivalence in cattle following single intramuscular or subcutaneous injection was determined. Plasma ceftiofur and desuroylceftiofur-related metabolites were measured by high performance liquid chromatography (HPLC). For both intramuscular and subcutaneous route similar systemic safety and therapeutic efficacy was shown in results. (Brown et al., 2000)
The pharmacokinetics of ceftiofur sodium after IM and SC administration in green iguanas was determined by Benson et al., 2003. Ceftiofur free-acid equivalents were measured via high-performance liquid chromatography. Ceftiofur free-acid equivalent concentrations were maintained $\geq$ 2 µg/mL for > 24 hours via both routes. It was suggested that the dosing schedule for ceftiofur sodium in green iguanas for microbes susceptible at > 2 µg/mL would be 5 mg/kg, IM or SC, every 24 hours.

The distribution of ceftiofur after single subcutaneous injection in ducks was evaluated. Two different doses of ceftiofur were given to two groups of ducks. Ducks were sacrificed on different days and blood as well as tissue samples from muscles, liver, kidney were collected. The concentrations of desfuroylceftiofur acetamide (DCA) and ceftiofur was determined. The concentrations of desfuroylceftiofur acetamide (DCA) were lower than 0.05 µg CFAE/g in all tissues on day 2nd post treatment. The concentration on day 1st was undetectable with less dose while with high dose i.e. 4 mg/kg DCA concentration was not detected on day 2nd. (Chung et al., 2007)

Mayer et al. (2009) determined the pharmacokinetics of ceftiofur sodium in foals and its concentration in different fluids present in body after intravenous administration.Minimum inhibitory concentration (MIC) against various bacterial pathogens common in equines was also determined. Concentrations of desfuroylceftiofur acetamide (DCA) were determined in synovial fluid, CSF, plasma and urine samples. UPLC-MS/MS was used to measure concentration in samples. For comparison microbiological assay was also used to measure concentration for same plasma samples. Results showed that cerebrospinal fluid was having significantly low concentration of DCA after multiple i.v. doses as compared to plasma DCA concentration In addition; administration of ceftiofur sodium @ 5 mg/kg by intravenous route might render

effective coverage against susceptible bacteria and would be helpful for treatment of such infections.

Liu et al. (2011) demonstrated the preparation and pharmacokinetics of ceftiofur sodium liposomes in cows. The objective of this study was to prepare ceftiofur sodium liposomes and assess their physical properties, stability, antibacterial effects, and pharmacokinetics. The findings of the researchers showed that this liposome preparation provided therapeutically effective plasma concentrations for a longer duration than with the drug alone, making it more effective and convenient for use in treating bovine mastitis that requires long duration maintenance of therapeutic plasma concentrations.

Pharmacokinetics of ceftiofur crystalline-free acid (CCFA) sterile suspension in the equine was investigated by Collard et al., 2011. Absolute bioavailability and dose proportionality studies were performed with ceftiofur in horses. Non-compartmental and mixed-effect modeling procedures were used to assess pharmacokinetics (PK). CCFA was well absorbed with a bioavailability of 100%. AUC(0-∞) and C(max) increased in a dose-related manner following administration of the two doses of CCFA at 3.3, 6.6, and 13.2 mg/kg. Simulations with the nonlinear mixed-effect PK model predicted that more than 97.5% of horses will have plasma ceftiofur equivalent concentrations >0.2 µg/mL for 96 h after the second 6.6 mg/kg dose of CCFA.

Pharmacokinetic evaluation of ceftiofur crystalline free acid in California sea lion was conducted by Meegan et al., 2013. . High performance liquid chromatography (HPLC) with tandem MS was used to measure concentration of ceftiofur and metabolites were maximum 24 hour after administration of ceftiofur. It was suggested that single intramuscular injection of ceftiofur crystalline free acid at the dose rate of 6.6 mg/kg would be maintain drug level 0.6lg/ml in plasma for 5 days.

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