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Ceftiofur and its Metabolites: Instability in the Right Places

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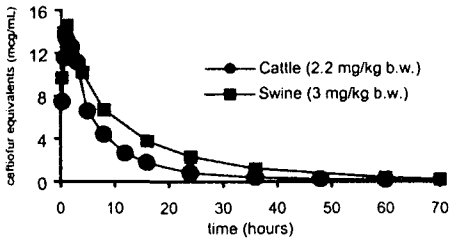
Ceftiofur is late-generation cephalosporin solely developed for veterinary therapeutic use. During the 12 years since its introduction for food animal use, surveys suggest that the incidence of veterinary and food-borne pathogens with decreased susceptibility to ceftiofur is still very low. This paper assesses the microbiological safety of ceftiofur with respect to current susceptibility patterns of pathogens, and inherent chemical and biological factors that aid in maintaining its effectiveness.

The ceftiofur minimum inhibitory concentrations (MICs) for targeted respiratory pathogens and salmonella[1-5], and the metabolism and fate studies of ceftiofur are reviewed[6-16]. The incidence of ceftiofur susceptibility among targeted respiratory pathogens for swine has remained at 100% in our surveys, with MIC values well below clinical susceptibility breakpoint (MIC value $\leq$2.0 ug/ml) approved by the National Committee for Clinical Laboratory Standards. Following parenteral injection, ceftiofur is rapidly metabolized (systemic half life less than 10 minutes) to desfuroyl ceftiofur (DFC), the primary, microbiologically active metabolite. The plasma concentrations of microbiologically active metabolites far exceed the MIC_{90} of target pathogens over a 24 hour dosing interval (Figure 1). Thus, the pharmacokinetic/pharmacodynamic properties of ceftiofur may work to minimize the potential for resistance emergence during the course of therapy, and may contribute to the observed high susceptibility rates.

Figure 1. Plasma levels of ceftiofur metabolites over time, after a single dose of ceftiofur. Dashed line shows the Salmonella cholerasuis MIC_{90} (1 ug/mL). *Pasteurella multocida* and *Actobacillus pleuropneumoniae* MIC_{90}'s are lower ($\leq$0.03 ug/mL).



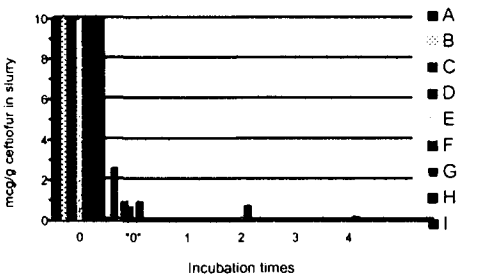
Another important attribute of ceftiofur is its instability upon elimination from the animal. Microbiologically active residues are a minor component of residues in feces. Their concentrations are at or below detection limits in fecal samples from animals receiving treatments. Urinary residues are inactivated readily in animal excreta when incubated aerobically (Table 1)[16].

Table 1. Ceftiofur residues in feces of 6 cattle dosed with [^{14}C]-Ceftiofur (5 daily doses, 2.2 mg/kg).

Animal No.	Avg fecal concentration (µg/g) of ceftiofur residue	
	Total	Microbiologically Active
1	6.2	$\leq$0.1
2	3.8	$\leq$0.1
3	5.5	$\leq$0.1
4	7.4	$\leq$0.1
5	4.5	$\leq$0.1
6	3.6	$\leq$0.1

Ceftiofur inactivation also occurs rapidly upon anaerobic incubation in human fecal slurries (Fig 2). Finally, ceftiofur is inactivated via hydrolytic and photolytic mechanisms, and is rapidly inactivated and mineralized ("degraded") to carbon dioxide in soils[16].

Figure 2. Observed inactivation of ceftiofur added to individual fecal samples from healthy human donors. "0" time is the time that it takes to process a sample immediately after ceftiofur is added to a fecal specimen[2].



The combination of having an appropriate pharmacokinetic and pharmacodynamic profile against target pathogens may have played a pivotal role in the low or undetectable incidence of ceftiofur resistance observed to date among targeted swine pathogens. The instability of ceftiofur and its residues upon excretion is desirable quality for any

antimicrobial drug. This instability minimizes environmental persistence, and in effect minimizes the likelihood of unwanted, bacterial exposure to this effective antimicrobial agent.

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