Ceftibuten Pharmacokinetics and Pharmacodynamics
Focus on Paediatric Use

Gregory L. Kearns1,2 and Ronald A. Young2,3

1 Department of Pediatrics, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA
2 Division of Pediatric Clinical Pharmacology, Arkansas Children’s Hospital, Little Rock, Arkansas, USA
3 Department of Pharmacy, Arkansas Children’s Hospital, Little Rock, Arkansas, USA

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Summary

Ceftibuten is an extended-spectrum, cephem antimicrobial agent formulated for oral administration. Ceftibuten is absorbed by carrier-mediated processes and passive diffusion. The absorption of ceftibuten is described adequately by a first-order process. Following oral administration, peak serum ceftibuten concentrations are reached within 2 to 3 hours. Although the absolute bioavailability of ceftibuten in humans is not known, its relative bioavailability indicates that there is relatively rapid and complete absorption of the drug. Administration of ceftibuten with food may decrease the rate of absorption and, in the case of high fat meals, may decrease the extent of absorption by approximately 20 to 30%. The results of limited studies indicate that the drug...
distributes well into various body tissues and fluids, with relatively high concentrations being achieved in organs that receive a significant portion of the cardiac output.

In adults with normal renal function or chronic renal failure, the apparent volume of distribution \((Vd/F)\) for ceftibuten ranges from 0.2 to 0.4 L/kg and the total plasma clearance \((CL/F)\) ranges from approximately 61 to 75 ml/min (3.7 to 4.5 L/h). Studies of ceftibuten elimination in adults have demonstrated a positive linear correlation between CL/F and creatinine clearance. Following administration of a single dose of ceftibuten, approximately 67 to 94% of the drug has been recovered in the urine unchanged. The elimination half-life \((t_{1/2})\) of ceftibuten in adults with normal renal function is approximately 2.5 hours. Significant accumulation of ceftibuten does not occur with repeated administration. Despite the fact that the mean time taken to achieve maximal serum concentration \((t_{max})\) [1.1 to 2 hours] and \(t_{1/2}\) (2.1 hours) following administration of a single dose of ceftibuten to infants and children were similar to values previously reported in adults, the \(Vd/F\) (0.42 L/kg) and \(CL/F\) (3.1 ml/h/kg) were considerably greater in children younger than 5 years. Additionally, the apparent nonrenal clearance of ceftibuten in paediatric patients (52% of CL/F) was greater than that reported for adults (approximately 32% of CL/F) with normal renal function. Thus, developmental differences appear to affect the pharmacokinetic profile of ceftibuten.

Ceftibuten has a wide spectrum of antimicrobial activity against both Gram-positive and Gram-negative pathogens, and is stable to hydrolysis by a large number of \(\beta\)-lactamases. Notable exceptions with regard to the Gram-positive spectrum for ceftibuten include relative or documented resistance for most strains of \(Listeria\), \(Staphylococcus aureus\), \(S. epidermidis\), penicillin-resistant strains of \(Streptococcus pneumonia\) and \(S. enterococcus\). In contrast, ceftibuten exhibits a high degree of activity against \(Haemophilus influenzae\), \(Moraxella catarrhalis\), \(Klebsiella pneumonia\), \(Neisseria\) spp. and \(Enterobacteriaceae\). In clinical trials, ceftibuten has demonstrated efficacy in the treatment of bronchitis, acute lower respiratory tract infections and urinary tract infections. Furthermore, the outcome following ceftibuten monotherapy was reported to be equal to that observed following therapy with conventional antibacterial agents. With the possible exception of diarrhoea (sometimes in conjunction with positive \(Clostridium difficile\) toxin), ceftibuten has been generally well tolerated without severe dose-limiting adverse effects.

The pharmacokinetic and \(in vitro\) antimicrobial activity support a role for ceftibuten in the treatment of otitis media, bronchopulmonary infections and uncomplicated urinary tract infections in infants and children. However, further paediatric trials of the drug will be required to determine optimal dosage, clinical efficacy and the adverse effect profile of the drug in paediatric patients.

Ceftibuten is an expanded spectrum cephem antimicrobial agent that is most appropriately classified as an oral third-generation cephalosporin. Ceftibuten has been described as 'a new, novel oral cephalosporin with pharmacokinetic qualities superior to that of cefixime and cefuroxime axetil' (Jones 1991).

In this article, we present a concise but complete review of the pharmacokinetics and pharmacodynamics of ceftibuten in humans, focusing on paediatrics. Published data describing the disposition characteristics of the drug, its \(in vitro\) activity relative to currently marketed oral cephalosporins of the same therapeutic class, and also differences in the disposition of ceftibuten in paediatric patients are discussed. In addition, the potential therapeutic role for ceftibuten is considered in view of similar cephalosporins (i.e. cefpodoxime proxetil, loracarbef, cefixime, cefadroxil) that have been formulated for oral administration to infants and children.

1. Physicochemical Characteristics of Ceftibuten and Analytical Considerations

Ceftibuten (fig. 1) has a chemical structure similar to cefixime, but markedly different to cefalexin, an oral first generation cephalosporin. Ceftibuten is an extremely polar weak acid, which is sparingly soluble in water. The drug is formulated for oral administration as the active \(cis\)-isomer (\(cis\)-ceftibuten), which can be converted in the serum and presumably, by the liver, to the \(trans\)-