Ceftibuten in ENT infections

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In India the most frequently occurring Upper Respiratory Tract infections seen are acute tonsillitis, acute sinusitis, acute pharyngitis and acute otitis media. These infections are so common that they lead to significant morbidity resulting in the loss of working hours or school days. Otitis media is mainly seen in young children - approximately 1/3 of children by their 3rd birthday experience 3 or more episodes. If inadequately treated, it could lead to a host of complications like suppuration, mastoiditis, hearing loss, facial paralysis, etc. Acute sinusitis, pharyngitis and tonsillitis generally occur in any age group and if, inappropriately treated, could lead to a chronic condition. It has been observed that the causative organisms involved in the above are most commonly-*Streptococcus pneumoniae*, *H. influenzae*, *M. catarrhalis* and occasionally Group A B Hemolytic *Streptococci*.

In the management of such conditions, when an ENT specialist selects an appropriate antibiotic, he looks for one, which should have :

- (i) a broad spectrum of activity that includes the above mentioned bacteria
- (ii) a convenient dosage form and
- (iii) minimal side effects

Ceftibuten is a broad spectrum third generation oral cephalosporin effective against most of the pathogens causing infections in the res-

piratory tract. Ceftibuten has an extended spectrum against a wide variety of enterobacteriae and selected gram positive organisms. It inhibits strains containing both the classic plasmid-mediated penicillinase and the new broad spectrum beta-lactamase. With the rise in beta-lactamase producing organisms, so also there is a rise in resistance. Hence, Ceftibuten could find an effective use in the above indications.

History

Schening-Plough Research Institute (U.S.A) is committed to its fight against infectious diseases. Its extensive anti-infective development programme has been focused on providing effective anti-microbial treatment, able to combat the emerging problems or the future. These problems include, in particular, new and complex microbial mechanisms of resistance. The introduction of Ceftibuten to the anti-infective arena, is a notable achievement for rational drug design. It marks the realisation of modern scientific research which has selected superior anti-infective characteristics through all stages of development from the molecule through to the final medicine.

Ceftibuten is a new once-daily oral cephalosporin. Its excellent pharmacokinetic characteristics, high degree of stability to extended beta-lactamases, remarkably good tolerability and favourable effects on the intestinal micro-

flora, go a long way towards meeting the exact requirements of an anti-infective agent, for the next decade.

Chemistry

Ceftibuten dihydrate is a semi-synthetic third generation cephalosporin. Its chemical formula is (+)-(6R, 7R)-7-[(z)-2-(2-amino-4 thiazoyl)-4-carboxycrotonamidel-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, dihydrate with a molecular wt = 446.63. In addition, inactive ingredients like micro-crystalline cellulose, sodium starch glycolate and magnesium stearate are present.

Mechanism of action

As with most beta-lactams antibiotics, the bactericidal activity of Ceftibuten results from the inhibition of bacterial cell wall synthesis, thus making it defective and osmotically unstable resulting in death of the bacteria.

Pharmacokinetics

Following oral administration, Ceftibuten is rapidly absorbed (75% - 90%) from the proximal gastro-intestinal tract [Barr et al, 1991]. The peak serum levels after 400 mg doses averages 17 mcg / ml & the time to reach peak concentration (Tmax) is 2 hours. Ceftibuten is about 60-64% protein bound [Barr et al, 1991, Fassbender, 1993, Nakashima et al, 1988] Following absorption, Ceftibuten penetrates many tissues and fluids. The maximum concentration is seen in the middle-ear fluid (71%) and in the respiratory tissues [Lin et al, 1990]. Distribution to the breast milk is usually undetectable after a 200 mg dose. Ceftibuten is not metabolised to any extent by the liver or bile. No active metabolites are found. The half-life of Ceftibuten is 2.5 - 3 hours and it is eliminated almost entirely as an intact molecule through the kidney. Elderly patients often have a reduced kidney function, consequently, elimination of drugs excreted by the kidney may be reduced and the elimination half-life may be

prolonged. Dosage adjustment is only necessary in those elderly patients with significant renal impairment. In children, the elimination is slightly more rapid, however, this does not require any dosage adjustment.

Microbiology

Bacterial organisms are considered susceptible to Ceftibuten if the minimum concentration required to inhibit 90% of the tested strains in vitro is < 8 mg / l. Most strains of enterobacteriaceae are susceptible to Ceftibuten, including *Citrobacteria diversus*, *Escherichia coli*, *Klebsiella oxytoca*, *K. pneumoniae*, *Proteus mirabilis*, *P. vulgaris*, *Providencia rettgeri*, *P. stuarti*, *Salmonella* spp, *Shigella* spp and *Yersinia enterocolitica* [Bauemfeind 1991, Shawar et al-1989, Verbist et al- 1991, Debbia-1992, Jones et al 1988 & Neu, 1993]. *M. morganii* and *Serratia marcescens* are moderately susceptible, whereas the majority of strains of *C. freundii*, *E. aerogenes* and *E. cloacae* are resistant. Other gram negative pathogens including beta-lactamase positive and negative strains of *H. influenzae* and *M. catarrhalis*, *N. gonorrhoea* and *N. meningitidis* are susceptible to Ceftibuten.

Beta-hemolytic streptococci groups A, C, F & G are also highly susceptible to Ceftibuten. It is seen that Ceftibuten is stable to hydrolysis to a majority of extended spectrum beta-lactamases produced by *E. coli* and *K.pneumoniae*.

Clinical efficacy in ENT infections

Respiratory tract infections remain a major cause of morbidity in infants and children in India. Though a vast majority are viral in origin, those that are bacterial often require effective antibiotic therapy. It is seen that Ceftibuten performed equal to or superior to comparator agents in large clinical trials. The cure and improvement rates in pharyngitis, otitis media and sinusitis exceeded 90%.

Effectiveness of Ceftibuten in acknowledged against aerobes such as *S. pneumonia*, *M. Catarrhalis* and *H. influenzae* in acute, mixed and chronic infections. Compared with other agents, Ceftibuten has one of the most comprehensive ranges of antibacterial coverage for acute otitis media in children. In three studies in children with acute otitis media, Ceftibuten 9 mg / kg / day, once daily for 10 days showed clinical and bacteriological efficacy which was similar to that of cefaclor or amoxicillin / clavulanic acid 40 mg / kg / day given thrice daily and with less side effects [Blummer et al, 1993 & McLinn et al, 1993, Gooch 1997]. Ceftibuten 9 mg / kg / day was significantly more effective than phenoxymethylpenicillin (penicillin V) 25 mg / kg / day administered in 3 divided doses to children and adolescents with Group A beta-hemolytic streptococcal pharyngitis achieving clinical response and bacteriological eradication in 97 vs 89% and 91 vs 80% of patients respectively [Pichichero et al, 1993]. Clinical responses occurred in all patients with bacterial sinusitis (clinical cure

in 68%) treated with Ceftibuten 400 mg once daily which was similar to the response rate in patients treated with Amoxicillin / clavulanic acid 500 mg three times daily with less side effects [De Abate et al, 1993]. In another recent trial comparing Ceftibuten once daily with Amoxicillin / Clavulanic acid 3 times a day, it was observed that Ceftibuten was equally effective & well tolerated [Sterkers et al, 1997]

Conclusions

From the above literature it can be seen that Ceftibuten with its broad spectrum antibacterial activity, stability to B lactamase inactivation, good oral absorption, once daily dosing & an outstanding safety profile could make it an important drug for the ENT specialist to fight infections.

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