Efficacy and Tolerability of Cefixime in Otitis Media
A Multicentre Study in over 25 000 Children

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Summary
A large scale multicentre clinical study was undertaken to assess the efficacy and tolerability of cefixime in the treatment of acute otitis media in children. A total of 25 863 evaluable children with acute otitis media received cefixime 8 mg/kg once daily for at least 10 days.

At the end of treatment, 86% of patients were considered to be either cured or improved. These results are consistent with those achieved with cefixime in controlled clinical trials. Adverse effects were reported in 11.5% of patients, but were judged to be related to cefixime therapy in only 9.4% of patients.

The results of this study demonstrate that cefixime is an effective and well tolerated treatment for acute otitis media in children.

Otitis media is one of the most common infectious diseases of childhood. Its sequelae, which include hearing loss, are significant health concerns. Standard therapy has been treatment with either ampicillin or amoxicillin; however, with the increasing incidence of otitis media caused by ß-lactamase-producing \textit{Haemophilus influenzae} and \textit{Branhamella (Moraxella) catarrhalis}, this may no longer be appropriate (Schwartz & Rodriguez 1989).

Cefixime, a new oral third generation cephalosporin, is currently available for the treatment of otitis media in the United States. It has a broad spectrum of activity against Gram-positive and Gram-negative organisms, and is particularly active against the major pathogens causing otitis media.

Additionally, cefixime can be administered once a day, which can lead to improved compliance. Hussar (1987) reported lack of compliance in up to 60% of patients with a 3-times daily dosage regimen and in 30% with a twice-daily regimen, while only 7% failed to take medications prescribed once daily.

We therefore conducted a large scale clinical study to evaluate the efficacy and tolerability of cefixime in the treatment of acute otitis media in children.

1. Patients and Methods

This was an open multicentre study of paediatric patients aged at least 6 months with a clinical diagnosis of acute otitis media. Patients were evaluated by the treating physician at the initial visit and, if eligible, entered into the study. Those with a history of gastrointestinal illness or noncompliance, allergy to cephalosporins or previous cefixime therapy were excluded. Cefixime was given at a dosage of 8 mg/kg for at least 10 days and clinical assessment was repeated at the end of therapy. A long term follow-up at 14 to 21 days after completion of therapy was desirable but not manda-
Table I. Gastrointestinal adverse effects reported in 27 714 children with otitis media treated with cefixime 8 mg/kg once daily for at least 10 days

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Incidence (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>6.3</td>
</tr>
<tr>
<td>Loose/frequent stools</td>
<td>1.0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0.4</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>0.1</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.09</td>
</tr>
<tr>
<td>Flatulence</td>
<td>0.02</td>
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</tbody>
</table>

A total of 3567 physicians participated in the study and enrolled 30 880 patients, of whom 27 714 completed at least 2 visits and were therefore evaluable for efficacy and tolerability. Approximately equal numbers of boys (53.4%) and girls (46.6%) were enrolled, most of whom were Caucasian (82.9%), Blacks represented 7.8%, Hispanics 6.2% and Orientals 1.3%, of the study population.

The majority of patients (83%) were between 6 months and 6 years of age, with 44.4% between the ages of 6 months and 2 years. Most had either just failed a previous course of antibiotic therapy (30.2%) or had experienced an episode of otitis media within the previous 2 months (33.8%).

Diagnostic criteria for otitis media included abnormal otoscopic findings in 95.8% of patients and clinical symptoms in 80.9%. Tympanograms or tympanocentesis were only performed in a minority of cases (6.6 and 0.2% of patients, respectively). During otoscopic examination, 88.9% of patients were found to have inflammation, 56.1% effusion, and 43.9% bulging tympanic membranes.

2. Results

At the end of therapy, 22 184 of the 27 714 evaluable patients (80%) were judged by their treating physicians to be either cured or improved, while 3679 (13.3%) were considered to have failed therapy or to have had an insufficient response. The remaining 1851 (6.7%) patients did not have outcomes specifically documented. Analysis of data from the 25 863 patients whose clinical status at the completion of therapy could be determined showed that 86% were cured/improved and 14% did not respond adequately.

Long term follow-up, obtained 2 to 3 weeks after the completion of therapy by telephoning the parents of the child, was available for 19 582 patients. 83% of patients were reported to be symptom free, while 17% had recurrence of symptoms.

Adverse events were documented in 11.7% (3200/27 714) of patients evaluable for efficacy, but these were judged by the treating physicians to be related to cefixime therapy in only 9.4% of patients (2583/27 714).

The most common adverse effects reported were gastrointestinal disturbances, which occurred in 9.0% of patients. The most frequently reported gastrointestinal adverse effect was diarrhoea (6.3%), with an additional 1.0% of patients experiencing loose or frequent stools. The remaining significant abdominal complaints comprised abdominal pain, dyspepsia, nausea, and flatulence (table I). The second most commonly reported adverse events were related to the skin and skin structures (2%), with rash (1.5%) most frequently seen.

3. Discussion

Initial antimicrobial therapy of acute otitis media usually consists of either ampicillin or amoxicillin. However, an increasing number of infections appear to be caused by β-lactamase-producing organisms (Kovatch et al. 1983; McLeod et al. 1985; Van Hare et al. 1987), which are resistant to ampicillin or amoxicillin. The efficacy of cefixime in this open study of over 27 000 patients with acute otitis media was comparable to that in controlled clinical trials of cefixime and adverse events were fewer. It can therefore be concluded that cefixime is an effective and well tolerated treatment for acute otitis media.