Penetration of azithromycin into middle ear effusions in acute and secretory otitis media in children

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In an open-label study, the concentrations of azithromycin in middle ear effusions and plasma were determined in 29 children between 1 and 8 years of age with a diagnosis of either secretory otitis media of at least 1 month's duration or acute otitis media. Azithromycin (10 mg/kg) was administered as a single dose 12, 24 or 48 h before the insertion of tympanostomy tubes to 17 children with secretory otitis media and once daily for 5 days (10 mg/kg on day 1, 5 mg/kg on days 2-5) to 12 children with acute otitis media. In the 16 evaluable patients with secretory otitis media, azithromycin penetrated middle ear effusions, with group mean concentrations approximately two orders of magnitude greater than the concurrent plasma concentrations 12, 24 and 48 h after administration. Similar plasma:effusion ratios were found 24 and 48 h after starting once-daily therapy in 10 evaluable patients with acute otitis media.

Introduction

Otitis media is a very common community-acquired paediatric infection, especially during the first years of life. Few children escape this disease and recurrent attacks are frequent (Pukander, Karma & Sipila, 1982). It accounts for approximately 8% of all of the respiratory tract diagnoses made in Finland in any one year (Peltola, 1982). In children with both acute otitis media with effusion (AOME) and secretory otitis media (SOM), Streptococcus pneumoniae and Haemophilus influenzae are the predominant pathogens, responsible for more than 50% of cases. Culture of middle ear fluid specimens obtained by tympanocentesis from children with AOME has revealed the presence of bacteria in up to 74% of cases, the commonest isolates being S. pneumoniae (35-50% of cases) and H. influenzae (12-25% of cases; Karma et al., 1980; Nelson, 1984). A third pathogen that is becoming increasingly important is Moraxella catarrhalis (Bluestone, 1982, 1989; Schaad, 1993). It has also been reported that Chlamydia pneumoniae may sometimes be a cause of middle ear disease (Ogawa, Hashiguchi & Kazuyama, 1992).

Penicillin has traditionally been used as treatment of common community-acquired paediatric infections, but there is increasing evidence the spread of resistant strains of S. pneumoniae (Reichler et al., 1992). Furthermore, the percentage of β-lactamase-producing strains of H. influenzae is 15-30%, and more than 90% of M. catarrhalis strains are β-lactamase-positive (Poole, 1993). Patients infected with these pathogens...
cannot be successfully treated with β-lactamase-susceptible agents (Van Hare et al., 1987) and suitable alternative therapies are, therefore, required for the treatment of these conditions.

Azithromycin is a recently developed antibacterial agent that is structurally related to erythromycin, but with an improved spectrum of activity against Gram-negative bacteria, such as *H. influenzae* and *M. catarrhalis*, although it retains the characteristic macrolide activity against Gram-positive organisms (Retsema et al., 1987; Hardy et al., 1988). The MIC₉₀ of azithromycin is, for example, 0.06 mg/L against *S. pneumoniae*, which is similar to that of erythromycin, and 1.0 mg/L against non-multiresistant strains of *Staphylococcus aureus*. Against *H. influenzae* and *M. catarrhalis*, however, the MIC₉₀ for azithromycin are 0.5 and 0.03 mg/L respectively; this is about two to four times less than the corresponding MICs for erythromycin (Retsema et al., 1987; Dunkin, Jones & Howard, 1988; Hardy et al., 1988; Maskell, Sefton & Williams, 1990). In addition, azithromycin possesses superior in-vitro activity to other recently developed macrolides—clarithromycin and roxithromycin—against *H. influenzae* and *M. catarrhalis* (Barry, Jones & Thornsberry, 1988; Fernandes & Hardy, 1988). A further marginal feature of azithromycin is its good in-vitro activity against *C. pneumoniae* (Chirgwin, Roblin & Hammerschlag, 1989).

Pharmacokinetic studies in adults have shown that, following the administration of a single dose, azithromycin penetrates rapidly into upper respiratory tract tissues (Foulds, Shepard & Johnson, 1990). As a consequence of the rapid tissue uptake, concurrent levels in plasma are 10- to 100-fold lower than those in tissues. Concentrations in tonsil and sinus mucosa, for example, exceed the MICs for many common respiratory pathogens and remain elevated for several days after administration.

The clinical consequences of this favourable pharmacokinetic profile have been demonstrated in a number of studies, which have shown that a once-daily dose of azithromycin administered over a short period of either 3 or 5 days achieves high rates of clinical cure and bacteriological eradication in children with upper respiratory tract infections, including otitis media (Pestalozza, Ciocca & Facchini, 1992; Daniel, 1993; Mohs et al., 1993; Schaad, 1993).

The aim of the present study was to determine the extent of penetration of azithromycin into middle ear effusions in children with SOM scheduled to undergo surgical insertion of tympanostomy tubes and in children with AOME.

**Patients and methods**

**Patients**

Children of either sex between the ages of 1 and 6 years were included in the SOM groups of the study, if they had middle ear effusion of at least one month's duration, and were scheduled for insertion of tympanostomy tubes. Boys or girls (age range 1–8 years) characterized by the presence of middle ear effusion and at least one of the following acute signs or symptoms (fever, otalgia, tugging at or rubbing of the ear, and/or otorrhoea not caused by external otitis or a current respiratory tract infection) were eligible for inclusion in the AOME groups.

Patients were excluded from the study if they had known hypersensitivity to macrolide antibiotics, evidence or history of haematological, renal, cardiovascular,
hepatic or metabolic disease, or presence of any disease likely to impair azithromycin absorption; or if the patient received concomitant treatment with theophylline, carbamazepine, prednisolone, digitalis, ergotamine or warfarin. Other treatment not permitted was any macrolide antibiotic up to 7 days before or during the study period, or any experimental drug during the 1-month period preceding to the study.

The study was conducted according to the Declaration of Helsinki (1964) and the Tokyo (1975) and Venice (1983) revisions, and informed consent was obtained from the patient's parents or guardians. Local ethical committee approval was also obtained.

**Administration of azithromycin**

Patients were divided into five groups, each containing a minimum of five patients. Groups 1–3 included children with SOM, who received a single dose of azithromycin (10 mg/kg body weight) as a 40 mg/mL aqueous suspension 12, 24 or 48 h before the scheduled insertion of tympanostomy tubes. Groups 4 and 5 consisted of children with AOME, who were treated with a 5-day regimen: an initial oral dose of 10 mg/kg azithromycin on day 1 and a once-daily dose of 5 mg/kg on days 2–5. No food or fat-containing drinks were taken for 2 h before or 1 h after the administration of azithromycin.

**Sample collection**

In patients with SOM (groups 1–3), specimens of middle ear effusions were collected during tympanostomy performed under general anaesthesia. Blood samples were also obtained immediately before azithromycin administration and at the same time as the surgery. In patients with AOME, middle ear effusions were aspirated by myringotomy under local anaesthesia either 24 h (group 4) or 48 h (group 5) after the first dose of azithromycin had been administered. All plasma specimens and samples of middle ear effusions were stored at —70°C until azithromycin concentrations were determined.

**Measurement of azithromycin concentrations**

Azithromycin concentrations in effusion samples and plasma were assayed by reversed-phase high-performance liquid chromatography, using azithromycin as the internal standard (Shepard, 1987). The lower limit of quantification was set at 0.02 mg/L azithromycin for both assay of plasma and middle ear effusions; concentrations below the lower limit were assumed to be 0 mg/L. To improve accuracy, the calibration line was divided into low (0.02–0.05 mg/L) and high (0.10–1.00 mg/L) ranges with concentrations of 0.5 mg/L or greater measured on the high range and concentrations below 0.5 mg/L measured on the lower range. Concentrations of azithromycin in middle ear effusions that exceeded the higher calibration range were estimated by extrapolation of the calibration line.

**Safety assessments**

A follow-up examination was performed for the SOM children on day 6 and for the AOME children on day 12–15. At these review visits, in addition to the relevant clinical data, all observed or volunteered adverse experiences were recorded together with details of severity (mild, moderate or severe), time of onset, duration and any symptomatic therapy required. Blood and urine samples for routine haematological and
biochemical safety analyses were also collected before azithromycin administration and during these review visits.

Results

A total of 29 children were enrolled in the study, 17 with SOM and 12 with AOME. The groups were similar with respect to mean age, age range and distribution of sexes (Table I). All but one of the 17 patients who received a single dose of azithromycin were evaluable; one child was excluded from evaluation because of the absence of any middle ear effusion at the time of surgery. Among the 12 children with AOME who received the 5-day regimen, ten were evaluable. Of the two patients excluded from the pharmacokinetic evaluation, one (group 4), who was scheduled for sample collection 24 h after initiation of azithromycin therapy, was withdrawn for reasons unrelated to the study drug and a second, in the 48-h group (group 5), was not evaluable because a middle ear effusion was not present at myringotomy.

Pharmacokinetics

The mean concentrations of azithromycin in plasma before oral administration and in plasma and middle ear effusions 12, 24 or 48 h after administration to patients undergoing surgery for SOM are shown in Table II. For the five patients from whom samples were obtained 12 h after receiving a single dose of azithromycin (group 1), the azalide was detected in two effusions. All six patients in group 2 and all but one in group

Table II. Mean azithromycin concentrations in plasma before and in plasma and middle ear effusions 12 (group 1), 24 (group 2), or 48 h (group 3) after oral administration of 10 mg/kg azithromycin to children with secretory otitis media

<table>
<thead>
<tr>
<th>Time</th>
<th>Plasma (mg/L)</th>
<th>Effusion (mg/L)</th>
<th>Plasma:effusion ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-administration (groups 1, 2 &amp; 3; n = 16)</td>
<td>&lt; 0.02</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>12 h post-administration (group 1; n = 5)</td>
<td>0.013</td>
<td>1.02</td>
<td>1:78</td>
</tr>
<tr>
<td>24 h post-administration (group 2; n = 6)</td>
<td>0.034</td>
<td>3.97</td>
<td>1:117</td>
</tr>
<tr>
<td>48 h post-administration (group 3; n = 5)</td>
<td>&lt; 0.004</td>
<td>1.42</td>
<td>1:355</td>
</tr>
</tbody>
</table>
3 had detectable levels of azithromycin in middle ear effusions 24 and 48 h, respectively, after receiving a single dose of 10 mg/kg azithromycin. In all cases where azithromycin was present in middle ear effusions, the concentrations were in the higher range of the calibration line with many individual concentrations exceeding the upper limit of 1.0 mg/L. In contrast, plasma concentrations of azithromycin were detected in a lower proportion of patients overall and, when detectable, were in the lower range of the calibration line. In all three groups, the mean concentrations of azithromycin in middle ear effusions were approximately two orders of magnitude greater than in plasma samples simultaneously obtained 12, 24 or 48 h after the administration of a single dose of azithromycin.

Table III shows the mean azithromycin concentrations in both plasma and middle ear effusions of patients with AOME who were to be treated with a 5-day regimen. At 24 h after the start of therapy (group 4), azithromycin was present in the middle ear effusions of all five evaluable patients and in four of the five evaluable patients at 48 h after the start of therapy (group 5); the effusion sample from one child in this group was not available. At both 24 and 48 h after the start of therapy, concentrations of azithromycin in middle ear effusions were again approximately two orders of magnitude greater than those in plasma obtained at the same time.

An assessment of the clinical response of the 11 evaluable patients with acute otitis media who completed the 5-day course of azithromycin therapy showed that nine were cured within 12–15 days; clinical improvement was observed in the remaining two patients.

**Safety**

All 29 patients enrolled in the study received at least one dose of azithromycin and were included in the safety analysis. The overall frequencies of treatment-related adverse events and laboratory test abnormalities are summarized in Table IV.

A total of three patients with AOME and two patients with SOM experienced adverse events. All were associated with the gastrointestinal system and were classified as mild. The three patients with AOME who experienced an event had diarrhoea, and in one patient this was accompanied by abdominal pain. Of the two patients with SOM experiencing adverse events, one had diarrhoea and the other flatulence. No patients were withdrawn from the study because of treatment-related adverse events.

Clinically significant changes in haematology, possibly related to treatment with azithromycin, were detected in three patients with SOM. These included an increased eosinophil count in one patient, an increased lymphocyte count in a second, and a decreased neutrophil count in a third.

Table III. Mean azithromycin concentrations in plasma before treatment and in plasma and middle ear effusions 24 or 48 h after the start of 5-day, once-daily oral administration to children with acute otitis media with effusion

<table>
<thead>
<tr>
<th></th>
<th>Plasma (mg/L)</th>
<th>Effusion (mg/L)</th>
<th>Plasma:effusion ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment (groups 4 &amp; 5; n = 10)</td>
<td>&lt; 0.02</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>24 h post-treatment (group 4; n = 5)</td>
<td>0.043</td>
<td>8.61</td>
<td>1:200</td>
</tr>
<tr>
<td>48 h post-treatment (group 5; n = 5)</td>
<td>0.026</td>
<td>9.43</td>
<td>1:363</td>
</tr>
</tbody>
</table>
Table IV. Frequencies of treatment-related side-effects and laboratory test abnormalities

<table>
<thead>
<tr>
<th>Patients</th>
<th>Secretory otitis media (single dose)</th>
<th>Acute otitis media (5-day regimen)</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. evaluated</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>no. with side-effects</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>no. withdrawn</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>no. with laboratory test abnormalities</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

Side-effects
- diarrhoea: 1 (1 single dose) / 3 (5-day regimen)
- abdominal pain: 0 (1 single dose) / 1 (5-day regimen)
- flatulence: 1 (1 single dose) / 0 (5-day regimen)

Discussion

Although it has been proposed that symptomatic treatment of non-complicated AOME may be sufficient in selected cases (van Buchem, Dunk & van't Hof, 1981), it is generally accepted that antibiotic therapy produces an improved clinical response. For an antibacterial agent to be effective it must possess in-vitro activity against those pathogens most frequently responsible for the condition. In addition, the agent should penetrate the middle ear fluid (McCracken, 1987) and supra-MIC levels in the fluid should be sustained (Baron & Bégé, 1991).

The results of the present open-label study show that, despite concentrations in plasma being low, azithromycin penetrates the middle ear effusions in patients with AOME or SOM. Mean concentrations of azithromycin in secretory effusions were approximately two orders of magnitude greater than in simultaneously obtained plasma samples 12, 24 or 48 h after a single dose. The high concentrations of azithromycin in acute middle ear effusions 48 h after the start of treatment show that azithromycin levels are sustained in tissue fluid even though concurrent plasma levels are barely detectable. A similar pattern of penetration of azithromycin into middle ear effusions was noted when children with AOME were studied, and again effusion levels were two orders of magnitude greater than those in plasma.

The pharmacokinetics of azithromycin in plasma and middle ear effusions observed in this study are comparable to the results obtained in studies conducted in adults, which have shown rapid penetration of azithromycin into the tissues and extravascular fluids of both the upper and lower respiratory tracts together with its slow elimination (Baldwin et al., 1990; Foulds et al., 1991; Morris et al., 1991). It is the long half-life of azithromycin in tissues and extravascular fluids that provides the rationale for the once-daily, short-course regimen (Foulds & Johnson, 1993).

The importance of the cellular kinetics of azithromycin in relation to its in-vivo efficacy in otitis media has also been clearly demonstrated in *H. influenzae*-induced middle ear infections in gerbils (Girard, Girard & Retsema, 1990) and chinchillas (Chan et al., 1988). Girard et al. (1990) observed that, following a single oral dose of azithromycin (100 mg/kg), antibiotic was still detectable at the site of infection after 48 h even though serum concentrations had declined to low levels. Unlike erythromycin or roxithromycin, in the gerbil model infected with *H. influenzae*, azithromycin exhibited this favourable characteristic which correlated with its enhanced bactericidal activity.
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against *H. influenzae* in comparison with the reference antibacterial agents (Retsema *et al.*, 1990).

Although many antibiotics penetrate the middle ear fluid, concentrations are not excessively high compared with those in plasma, as with azithromycin. Loracarbef levels in the middle ear fluid of patients with SOM, for example, were approximately 45% of those in plasma 2 h after administration (Kusmiesz *et al.*, 1990). Macrolides, except erythromycin, have been shown to be the antibacterial agents most readily able to penetrate the middle ear fluid. Concentrations of troleandomycin and josamycin exceeded those in serum, whereas penetration of amoxycillin was relatively poor (Bérézin *et al.*, 1985). Although, among children with SOM treated with 7.5 mg/kg clarithromycin twice daily for 7 days, concentrations of clarithromycin and the 14-hydroxy metabolite in middle ear effusion after 3 days were approximately twice those in serum, only about 50% of *H. influenzae* isolates were eradicated (Sunderberg & Cederberg, 1994). Markedly high miocamycin concentrations were also detected in middle ear fluid in patients with SOM 2 h after drug administration, but thereafter concentrations fell rapidly (Fraschini *et al.*, 1991). In none of these studies, however, did the concentration in middle ear fluid exceed that in serum by the same order of magnitude as observed with azithromycin in the present study. Another unique feature of azithromycin is that concentrations in middle ear fluid remained elevated over a prolonged period even after a single dose.

In the present study, azithromycin achieved clinical cure in nine of the 11 patients with acute otitis media treated once daily for 5 days; clinical improvement was seen in the remaining two patients. One reason for this relatively high rate of resolution of signs and symptoms may be that tympanocentesis was performed in all children. Other studies investigating the clinical efficacy of azithromycin in the treatment of both AOME and SOM have found it to produce correspondingly high rates of clinical cure when administered once-daily over a 3- or 5-day period to adults (Felstead *et al.*, 1991; Müller, 1993) and children (Pestalozza *et al.*, 1992; Daniel, 1993; Mohs *et al.*, 1993; Schaad, 1993).

Azithromycin was well tolerated by all patients in the present study, producing no serious side-effects and no patient was withdrawn from treatment for reasons related to azithromycin. Treadway & Pontani (1994), in a review including 1517 children treated with azithromycin and 1295 with comparator agents, showed a significantly lower frequency of side-effects and fewer withdrawals among the patients receiving azithromycin compared with other antibiotics conventionally used in the treatment of upper respiratory tract infections.

**References**


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