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Concentrations of azithromycin in tonsillar and/or adenoid tissue from paediatric patients

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Azithromycin levels in tonsillar and/or adenoid tissue were determined in children (1.6–7.5 years old) who were scheduled for surgical removal of their tonsils and/or adenoids. The children received azithromycin oral suspension 10 mg/kg once daily for 3 days. Tissue samples were obtained during surgery 1 ($n = 4$), 2 ($n = 5$), 4 ($n = 6$), or 8 ($n = 5$) days after the last dose of azithromycin. Serum samples were also obtained from four children in each of these groups at the time of surgery. Mean tissue concentrations of azithromycin were 10.33 ± 3.01, 7.21 ± 4.04, 9.30 ± 3.74 and 1.49 ± 0.48 mg/kg, respectively, 1, 2, 4 and 8 days after the last dose. At the corresponding times, serum concentrations were markedly lower: 47.25 ± 19.19, 14.00 ± 8.45, 8.00 ± 2.16 and <4 μg/L, respectively. The mean tissue:serum concentration ratios were, 227 ± 54, 547 ± 184 and 956 ± 355, respectively, 1, 2 and 4 days after treatment. No adverse events attributable to azithromycin were observed in any of the 23 children who had received at least one dose of azithromycin. The study shows that levels of azithromycin in tonsillar and adenoid tissue were consistently higher than in serum and remained elevated up to 8 days after the end of dosing, supporting the use of a short-course (3-day), once-daily regimen of azithromycin in the treatment of upper respiratory tract infections.

Introduction

Infectious pharyngitis/tonsillitis is very common in children. This condition, when of bacterial aetiology, is usually caused by *Streptococcus pyogenes* and is a major indication for the prescribing of oral antibacterial agents. Otitis media is another childhood upper respiratory tract infection that is frequently encountered in clinical practice, for which *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis* are the most common pathogens.

Standard therapy for streptococcal pharyngitis has been a 10-day oral regimen of penicillin V, given up to four times daily, and for otitis media the standard is a 10-day regimen of amoxycillin or ampicillin given three or four times daily. A 10-day, multiple-daily course of erythromycin has been used as an alternative when there is hypersensitivity to penicillins. However, the use of erythromycin has been limited, particularly in adults, by the high incidence of gastrointestinal side-effects (Pilot & Qin, 1988; Pechère, 1993). Furthermore, the protracted multiple-dose regimens of both

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penicillins and erythromycin may, particularly in children, result in poor compliance, with detrimental effects on treatment outcome.

Azithromycin is a macrolide antibacterial agent, structurally related to erythromycin (Bright *et al.*, 1988), but with improved in-vitro activity against Gram-negative pathogens, such as *H. influenzae* (Retsema *et al.*, 1987) and *M. catarrhalis* (Hardy *et al.*, 1988), and good activity against other pathogens, including *S. pyogenes* and *S. pneumoniae* (Retsema *et al.*, 1987).

Studies in adults have shown that the pharmacokinetic profile of azithromycin is characterized by high tissue concentrations, which are frequently more than 100 times those in serum. Azithromycin levels of 4.5 mg/kg have been achieved in tonsillar tissue, with a half-life of 76 h after two 250-mg doses at a 12-h interval (Foulds *et al.*, 1991). Extrapolations from these data established that once-daily dosing with 500 mg azithromycin for 3 days would maintain tonsillar levels of azithromycin at more than 2 mg/L for over 10 days, which is above the MIC_{90} of azithromycin against common upper respiratory tract pathogens (Foulds & Johnson, 1993).

This open-label study was designed to investigate azithromycin concentrations in the tonsils and/or adenoids of children scheduled for surgical removal of these tissues. The objectives were to confirm the pharmacokinetics of azithromycin determined in adults and support the use of a 3-day, once-daily oral dosage regimen in the treatment of upper respiratory tract infections.

Patients and methods

Patient selection

Children, of either sex, aged between 2 and 8 years, who were scheduled for surgical removal of their tonsils and/or adenoids were eligible for the study. The children had to be within the normal height and weight ranges for their age. Children were excluded from the study if they had a history of sensitivity to any macrolide antibiotic, had any condition that might affect drug absorption, were receiving or had received any other antimicrobial agent in the previous week, had received any experimental drug in the previous 4 weeks, or had evidence or a history of significant haematological, renal, hepatic, or cardiovascular disease.

Study design

This study was conducted with the approval of the institutional review board. After written informed consent had been obtained from the child's parents or legal guardian, a medical history was recorded and a physical examination performed. Children were allocated to one of four groups (groups I–IV) depending upon whether surgery was scheduled for 1, 2, 4 or 8 days after the final dose of azithromycin.

Parents or guardians were provided with bottles containing powder for oral suspension of azithromycin (900 mg/bottle); this was reconstituted in the investigator's office by adding 12 mL water. The child's parents or guardian were provided with a calibrated syringe so that the volume of suspension given could be precisely measured. Children received azithromycin oral suspension 10 mg/kg once daily for 3 consecutive days, 90 min before the evening meal. The parents or guardian were instructed to record

the amount of azithromycin given and the time of administration so that compliance could be monitored.

Azithromycin assay

Tissue and serum samples obtained at surgery were immediately frozen at −50°C until the analysis could be performed. Azithromycin concentrations were determined by high-performance liquid chromatography with electrochemical detection (Shepard *et al.*, 1987) at the Clinical Pharmacology Division of the Geneva University Hospital. The lower limit of detection of azithromycin in serum was considered to be 4 μg/L and in tissue 75 μg/kg.

Safety

All adverse events, whether reported spontaneously by the child, their parents or guardian, or observed by the investigator were recorded with details of day of onset, duration, severity (mild, moderate or severe), outcome and relationship to treatment (related, not related or uncertain/unknown).

Laboratory tests were performed before the first dose of study medication and at the time of surgery.

Statistical analysis

As this was an open-label non-randomized study only general descriptive statistics were used. Azithromycin tissue concentrations were calculated in mg/kg and serum concentrations in μg/L. One-way analysis of variance was used to compare mean azithromycin concentrations between groups (Spjotvol & Stoline, 1973).

Results

Patients

In total, 26 children were enroled in the study; of these 23, 1.6–7.5 years of age, received at least one dose of azithromycin. The baseline characteristics of children who received at least one dose of azithromycin are summarized in Table I. There were no significant differences in mean age, weight or height between the groups. Adenoidal hypertrophy was the reason for surgery in 21 children and five of these also had tonsillar

Table I. Baseline characteristics of patients

Characteristic	Group I ($n = 6$)	II ($n = 6$)	III ($n = 6$)	IV ($n = 5$)	Total ($n = 23$)
Male	3	4	4	3	14
Female	3	2	2	2	9
Mean age ± S.D. (years)	4.2 ± 1.2	4.9 ± 1.6	5.5 ± 2.3	5.1 ± 2.2	4.9 ± 1.8
Mean weight ± S.D. (kg)	15.1 ± 1.9	19.0 ± 4.2	18.9 ± 4.2	18.2 ± 5.3	17.8 ± 4.1
Mean weight ± S.D. (cm)	104 ± 7	111 ± 8	113 ± 16	109 ± 13	109 ± 11

hypertrophy; two children had tonsillar hypertrophy alone. Of these 23 children, 16 also had secretory otitis media.

In all, 21 children took the complete three-dose course of azithromycin. One patient in group I received only the second and third doses of azithromycin and another patient from group II was withdrawn after receiving one dose of azithromycin because of unrelated adverse events; both these patients were excluded from the statistical analysis of tissue and serum levels.

Patients in group I received their final doses of azithromycin 16–20 h (mean 17 h) before surgery, in group II the times to surgery were 39–63 h (mean 46 h) after dosing, in group III 88–91 h (mean 90 h) elapsed and in group IV 182–188 h (mean 185 h).

Azithromycin tissue concentrations

Azithromycin tissue concentrations were determined for 20 patients who received all three doses of azithromycin: four from tissues removed at 1 day post-treatment, five at 2 days; six at 4 days and five at 8 days (Table II). The azithromycin levels of one child assigned to group I (last dose of azithromycin 24 h before surgery) could not be assessed as her operation was cancelled. Adenoid tissue only was used from 15 patients, tonsillar tissue only from one patient and both tissues from four patients. Concentrations in adenoid and tonsillar tissue were similar. Mean azithromycin concentrations were 10.33 ± 3.01, 7.21 ± 4.04, 9.30 ± 3.74 and 1.49 ± 0.48 mg/kg, respectively, at 1, 2, 4 and 8 days after the final azithromycin dose. The ranges of azithromycin tissue levels 1, 2, 4 and 8 days after treatment were, respectively, 7.40–14.20, 2.00–11.50, 4.90–15.20 and 1.00–2.10 mg/kg. There was no significant difference in mean azithromycin levels between tissues taken at 4 days post-treatment and those obtained after 1 or 2 days. Azithromycin levels 8 days after treatment were significantly lower ($P < 0.005$) than those 1 day post-treatment: at the earlier assessments all tissue azithromycin concentrations were 2 mg/kg or more, whereas for the 8-day assessment tissue concentrations were between 1 and 2 mg/kg in all except one patient.

Azithromycin serum concentrations

Serum samples were obtained at the time of surgery from four children in each group. Mean serum azithromycin levels were 47.25 ± 19.19, 14.00 ± 8.45, 8.00 ± 2.16 and < 4 μg/L, respectively, at 1, 2, 4 and 8 days post-treatment. In contrast to tissue levels, serum concentrations were highest 1 day after the end of treatment and progressively decreased until after 8 days they were below the limits of detection.

Tissue:serum concentration ratios

Tissue:serum concentration ratios ranged from 187 to 302, 300 to 733 and 600 to 343, respectively, 1, 2 and 4 days post-treatment; the ratio could not be established in tissues assessed after 8 days because serum levels were below the limits of detection. The ratio was highest in the group assayed 4 days after treatment and was significantly higher ($P < 0.005$) than at 1 day after treatment.

Table II. Azithromycin concentration in tonsillar and/or adenoid tissue, and in serum 1, 2, 4 and 8 days after the end of a 3-day, once-daily oral azithromycin regimen in children

	Time post-treatment							
	1 day		2 days		4 days		8 days	
	mean	range	mean	range	mean	range	mean	range
Tissue concentrations (mg/kg)	10.33 ± 3.01 ($n = 4$)	7.40–14.20	7.21 ± 4.04 ($n = 5$)	2.00–11.50	9.30 ± 3.74 ($n = 6$)	4.90–15.20	1.49 ± 0.48 ($n = 5$)	1.00–2.10
Serum concentrations (μg/L)	47.25 ± 19.19 ($n = 4$)	37.0–76.00	14.00 ± 8.45 ($n = 4$)	7.00–24.00	8.00 ± 2.16 ($n = 4$)	5.00–10.00	<4 ($n = 4$)	NA
Tissue:serum ratio	227 ± 54	187–302	547 ± 184	300–733	956 ± 355	600–1343	NA	NA

NA, Not assessable.

Safety

None of the 23 patients who received at least one dose of azithromycin experienced adverse events attributable to azithromycin. One patient from group II, whose serum transaminases had been elevated before treatment, experienced nausea, vomiting, abdominal pain and diarrhoea on the day after the first dose of azithromycin. These adverse events were considered to be due to a mild concurrent hepatitis A infection and unrelated to study treatment. This patient was withdrawn from treatment after receiving one dose of azithromycin.

Discussion

A previous pharmacokinetic study has been conducted in adults given two 250-mg doses of azithromycin 12 h apart (Foulds *et al.*, 1991). Pharmacokinetic modelling of data from that and other studies (Foulds & Johnson, 1993) have suggested that a 3-day, once-daily regimen of 500 mg azithromycin maintains tonsillar levels of azithromycin above 2 mg/L for more than 10 days. The current study demonstrated that in children a 3-day, once-daily course of oral azithromycin achieved high azithromycin concentrations in tonsillar and/or adenoid tissue that were maintained for 8 days after the end of treatment and that the values were consistent with those predicted in adults. As in adults, azithromycin levels in tissue were consistently many times higher than in serum.

In this study, tonsillar and/or adenoid azithromycin levels exceeded the MIC_{90}s for many upper respiratory tract pathogens, including *S. pyogenes* (0.1 mg/L; Retsema *et al.*, 1987), *H. influenzae* (0.78 mg/L; Retsema *et al.*, 1987), *M. catarrhalis* (0.03–0.06 mg/L; Hardy *et al.*, 1988) and *S. pneumoniae* (0.05 mg/L; Retsema *et al.*, 1987), for up to 8 days after the end of treatment. Thus, the study supports the use of short-course, once-daily azithromycin regimens in children for the treatment of upper respiratory tract infections. A number of studies have already demonstrated the clinical efficacy of such 3-day, once-daily regimens of azithromycin in the treatment of upper respiratory tract infections in both children (Hamill, 1993; Weippl, 1993; Bottaro *et al.*, 1994) and adults (Müller, 1993), indicating that the high levels of azithromycin in the tissues of the upper respiratory tract produce clinical benefits.

For some years, it has been known that both adults (Gatley, 1968) and children (Bergman & Werner, 1963) are poorly compliant with anti-infective regimens that are more than one week in duration and involve multiple-daily dosing. The reasons are numerous, but the duration and frequency of dosing are among the most important (Greenberg, 1984; Cockburn *et al.*, 1987). Colcher & Bass (1972) showed that poor compliance is likely to lead to an unsatisfactory clinical outcome. An anti-infective agent with a simple dosing regimen, preferably once daily, combined with a short duration of treatment should improve patient compliance and ultimately clinical outcome. Azithromycin should, therefore, be more effective in the non-clinical trial environment than antibacterials with more prolonged and complex treatment regimens.

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