ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 1996, p. 2765–2768 Vol. 40, No. 12
0066-4804/96/$04.00+0

Prospective Open Randomized Study Comparing Efficacies and Safeties of a 3-Day Course of Azithromycin and a 10-Day Course of Erythromycin in Children with Community-Acquired Acute Lower Respiratory Tract Infections

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Received 7 February 1996/Returned for modification 9 July 1996/Accepted 26 September 1996

The efficacies and safeties of a 3-day, 3-dose course of azithromycin (10 mg/kg of body weight per day) and a 10-day, 30-dose course of erythromycin (40 mg/kg/day) for the treatment of acute lower respiratory tract infections in children were compared in an open randomized multicenter study. Sixty-eight of 85 evaluable patients (80%) had radiologically proven pneumonia, and 20% had bronchitis. Treatment success defined as cure or major improvement was achieved in 42 of 45 (93%) azithromycin recipients versus 36 of 40 (90%) erythromycin recipients. Adverse events were reported in 12 of 45 and 6 of 40 of the patients treated with azithromycin and erythromycin, respectively, a difference which was not statistically significant. In conclusion, a 3-day course of azithromycin is as effective as a 10-day course of erythromycin in the treatment of community-acquired lower respiratory tract infections in children, with comparable safety and acceptability profiles. This shorter treatment course might have a beneficial effect on compliance, especially in the pediatric age group.

Azithromycin is a novel semisynthetic azalide antibiotic that differs structurally from erythromycin in that it contains a methyl-substituted nitrogen at position 9a in the macrolide ring, resulting in interesting pharmacological properties, e.g., better acid stability, less protein binding, and good tissue and intracellular penetration (1). Additionally, the antibacterial spectrum and activity of azithromycin are extended compared with those of traditional macrolides, with improved potency against the most important causative organisms of nonviral lower respiratory tract infections (LRTI) in children (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*) (7). Azithromycin penetrates well into a variety of tissues, including those of the respiratory tract, and reaches adequate therapeutic concentrations in sputum. Moreover the pharmacokinetics of azithromycin in adults and children is characterized by a rapid and extensive movement of the drug into intracellular compartments, e.g., alveolar macrophages, resulting in tissue drug concentrations significantly higher than serum drug concentrations obtained concurrently. The high levels achieved in tissue are sustained above the MICs for the mentioned respiratory pathogens for 7 days after the last (third) dose (6, 9).

These advantageous pharmacokinetic properties and improved antimicrobial potency make azithromycin attractive for the treatment of community-acquired infections in childhood, where compliance with a classical 10-day course of antibiotics is often problematic. In this regard azithromycin has been shown to be effective for the treatment of upper respiratory infections (11), otitis media (5), and skin infections in childhood (8).

Community-acquired LRTI are an important clinical problem in pediatrics, for which oral outpatient treatment with beta-lactam antibiotics or macrolides is preferred. This paper reports on an open randomized multicenter trial comparing a 3-day (3-dose) course of azithromycin with a 10-day (30-dose) course of erythromycin in children with acute pneumonia or bronchitis.

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MATERIALS AND METHODS

Eighty-nine children between the ages of 2 and 16 years with a presumed diagnosis of community-acquired LRTI (pneumonia or bronchitis) were enrolled in an open comparative multicenter study. Patients were randomized to receive orally either azithromycin suspension at a once-daily dosage of 10 mg/kg of body weight to a maximum of 500 mg/day for 3 days or erythromycin suspension at a dosage of 40 mg/kg/day divided in three daily doses for 10 days. Block randomization was done at U-Gene Research, Utrecht, The Netherlands. The study protocol was approved by each hospital's Medical Ethical Committee for Human Studies. Informed consent was obtained for all patients from their parents or legal guardians.

Clinical evidence of acute LRTI was defined as the presence of at least three of the following symptoms: cough, tachypnea (respiratory rate > 20 breaths per min), rectal or oral temperature of $\geq 38°C$, leukocytosis (leukocyte count $\geq 12 \cdot 10^9$/liter), chest findings at physical examination suggestive of LRTI (rales, rhonchi, or signs of consolidation), and/or abnormal chest X-ray suggestive of LRTI.

Patients were excluded by the following conditions: inability to take oral medication, known hypersensitivity to erythromycin or azithromycin, cystic fibrosis, immunodeficiency, a leukocyte count of $< 3 \cdot 10^9$/liter, the requirement for supplemental oxygen, known or suspected bacteremia, nosocomial pneumonia, infection requiring alternative treatment or addition of another antibiotic, concomitant use of ergotamine or digitalis, past or present gastrointestinal disease affecting drug absorption, a known baseline pathogen resistant to the study drugs, or the use of antibiotics within 48 h prior to treatment.

Each child was clinically examined before treatment and on days 4 to 6 (first follow-up visit), days 10 to 14 (second follow-up visit), and days 25 to 30 (third follow-up visit) after study entry. Before treatment and at the second follow-up visit serum chemistry and hematology tests as well as a urinalysis were performed. These laboratory safety tests were repeated at the third follow-up visit if the tests at days 10 to 14 showed clinically relevant abnormalities. All children had a chest X-ray before treatment and at days 10 to 14. If it was still abnormal at the second follow-up visit, a control chest X-ray was repeated after 25 to 30 days.

All three follow-up visits included monitoring for possible side effects of the study medication. Medication (inhalation corticosteroids, bronchodilators, antipyretics, or expectorants, e.g.) in addition to the study drug was taken by 22 patients (49%) treated with azithromycin, who received a mean of 2.5 drugs, and

TABLE 1. Patient characteristics

Treatment group	No. of patients				Mean age [yr (SD)]
	Total	Male/female	With acute pneumonia	With acute bronchitis	
Azithromycin	45	28/17	34	11	4.9 (3.1)
Erythromycin	40	22/18	34	6	5.6 (3.3)

by 25 patients (62.5%) treated with erythromycin, who received a mean of 2.4 drugs. These differences were not statistically significant.

Bacteriological documentation of LRTI in children can be cumbersome. Sputum is difficult to obtain, while lower pharyngeal swabs are not always representative for the pathogens in the lower respiratory tract. Taking these limitations into account, lower pharyngeal swabs were obtained before and after treatment. Microorganisms were isolated and identified according to standard bacteriological methods. Antimicrobial susceptibility to the study drugs was assessed by a standard disc diffusion method. On the first and third visits blood samples were obtained for serologic determination. The presence and titers of antibodies against respiratory pathogens such as respiratory syncytial virus, influenza A and B virus, parainfluenza virus, adenovirus, *Coxiella burnettii*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae* were determined by standard indirect fluorescence assays. Seroconversion was defined as a fourfold or more rise in antibody titers, allowing a possible correlation with the concurrent illness. Clinical response to therapy was classified as follows: cure was defined as the complete remission of all pretreatment clinical signs and symptoms, improvement was defined as the amelioration of symptoms, and treatment failure was defined as unchanged or worsened clinical signs and symptoms. The patient had to take the complete course of study medication (3 days of azithromycin or 10 days of erythromycin) to be eligible for evaluation, unless there was clear evidence of therapeutic failure or presence of side effects necessitating withdrawal of the study drug.

Bacteriological response was graded as follows: eradication of the causative organisms when the second lower pharyngeal culture became negative for a possible baseline pathogen, colonization when the organism(s) present before and/or after treatment was considered to be not related to the present episode of illness, and indeterminate when it was not possible to evaluate the results bacteriologically.

Proportions within the two treatment groups were compared by the chi-square test and the two-tailed Fisher's exact test. For comparison of group means ± standard deviations of patient demographic and medical characteristics before study entry, Student's *t* test was used. A *P* value of less than or equal to 0.05 was considered statistically significant.

RESULTS

Of the 89 patients enrolled in the study, 85 were included in the final analysis. Two patients did not fulfill the inclusion criteria (one patient was less than 2 years old, and the second child had only two clinical signs and a normal chest X-ray), and two patients were lost to follow-up. The two treatment groups did not differ with respect to age, gender, or initial diagnosis (Table 1). Ninety-five percent of the patients (81 of 85) had an initial abnormal chest X-ray. Eighty percent (68 of 85) of the children had radiologically proven pneumonia (34 in each group). Seventeen patients (20%) were diagnosed with acute bronchitis (11 in the azithromycin group and 6 in the erythromycin group). These differences between the two groups were not statistically significant. The two study groups did not differ in initial or follow-up infectious laboratory parameters (C-reactive protein or total and differential leukocyte count) (data not shown).

Forty-five and 40 patients were treated with azithromycin and erythromycin, respectively. At the second follow-up visit after 10 to 14 days, 31 versus 27 patients in the azithromycin and erythromycin groups, respectively, were cured, 12 versus 9 were improved, and for 1 versus 4 treatment was considered to be a failure (Table 2). These differences were not statistically significant. One patient clinically deteriorated after 2 days of erythromycin treatment and was switched to intravenous therapy with cefuroxim. Another child had persistent respiratory symptoms and increasing leukocytosis at the second and third follow-up visits. A third patient had increasing radiological abnormalities and persistent clinical signs and was switched to amoxicillin-clavulanic acid. The fourth patient was not clinically improved after the 3 days of azithromycin, and trimethoprim-cotrimoxazol was prescribed from day 4 onwards. The last patient was clinically not improved at the second follow-up visit, and the 10-day course of erythromycin was followed by a course of amoxicillin-clavulanic acid.

At the third follow-up visit (after 25 to 30 days), 41 versus 33 patients were cured in the azithromycin versus erythromycin group, respectively, 1 versus 3 were improved, and 2 patients in the azithromycin group developed a new or recurrent LRTI within the study period. These differences were not statistically significant. The first patient with a relapse after azithromycin treatment for acute pneumonia had worsening of symptoms at the fourth visit. He was treated subsequently with amoxicillin-clavulanic acid. It is unclear why the symptoms recurred, but there was a history of nausea and vomiting during initial therapy. The second patient who relapsed had acute pneumonia with infiltrates in the right lower lobe. After improvement on visit three, his respiratory symptoms were worse at visit four. The trial drug was administered according to the treatment schedule, and vomiting had not occurred. No explanation could be found for this unfavorable outcome. Because the fourth visit was scheduled approximately 1 month after the inclusion date, it is possible that these two patients were reinfected rather than relapsed. The finding of *M. catarrhalis* in the nasopharynx during the initial visit of the first patient in contrast to four positive cultures for *H. influenzae* after the recurrence of symptoms supports this hypothesis. The second patient was colonized with *M. catarrhalis* and *S. pneumoniae* on both occasions.

There was no correlation between the clinical response and the age of the patients.

Although the majority of the treatment failures occurred in children less than 5 years old, the difference was not significant, possibly because of the small number of cases in which treatment failed.

Eighteen patients or their parents, 12 in the azithromycin group and 6 in the erythromycin group, reported at follow-up 31 adverse events possibly related to the study drug (Table 3). These differences were not significant. Most adverse events were gastrointestinal complaints (diarrhea, abdominal discomfort, and vomiting). Especially vomiting was more prevalent in the azithromycin group. One patient receiving azithromycin developed transient elevation of alanine transferase during treatment (maximum value, 50 IU/liter), returning to normal at the end of follow-up (20 IU/liter). One patient passed black stools once on day 7 of treatment with erythromycin. A test for occult blood was not performed.

TABLE 2. Clinical response

Response	No. of patients in group at:			
	Days 10–14		Days 25–30	
	Azithromycin	Erythromycin	Azithromycin	Erythromycin
Cure	31	27	41	33
Improvement	12	9	1	3
Failure	1	4	NA[a]	NA
Relapse	NA	NA	2	0
Total	44[b]	40	44	36

[a] NA, not applicable.
[b] One patient missed the third visit.

TABLE 3. Adverse events

Adverse event	No. of patients with adverse events while receiving:	
	Azithromycin (n = 12)	Erythromycin (n = 6)
Diarrhea	4	4
Vomiting	7	1
Nausea	4	
Abdominal discomfort	2	3
Flatulence	1	2
Black stool		1
Constipation	1	
Alanine transferase elevation	1	

For 12 patients two microorganisms were cultured from the lower pharynx before the start of therapy. Twenty patients had a positive culture for one organism, while no organisms were found in the pharyngeal swabs of 53 children. Table 4 lists the microorganisms isolated from the lower pharynx before treatment. All isolates were susceptible to azithromycin (disc diffusion test corresponding to an MIC of <2 μg/ml). Four *H. influenzae* isolates were susceptible to erythromycin (corresponding MIC <2 μg/ml), 11 had an intermediate susceptibility, and 3 were resistant (corresponding MIC $>$ 8 μg/ml). One *Haemophilus* isolate was not available for susceptibility testing. All *M. catarrhalis* and *S. pneumoniae* isolates were susceptible to both study drugs. One of four *Streptococcus pyogenes* isolates was intermediately susceptible to erythromycin, and so was the only *Staphylococcus aureus* isolate. No significant difference in the eradication by both study drugs for any of the isolates was seen. Paired serum samples for serological tests were available for 55 patients. Sixteen patients had a more than fourfold increase in specific titer for various microorganisms: four for parainfluenza virus, one for adenovirus, five for respiratory syncytial virus, three for influenza virus, and three for *Mycoplasma pneumoniae*. There were no differences in serology data between the azithromycin and erythromycin groups.

DISCUSSION

The present report shows an equal efficacy of a 3-day course of azithromycin and a 10-day course of erythromycin in the treatment of community-acquired LRTI in children. Both study drugs had comparable safety and acceptability patterns.

Pediatricians will often include an antibiotic in the treatment of acute LRTI. However, whether an antibiotic is needed remains controversial. To assess the value of antibiotics, it is important to know the likelihood of a bacterial versus viral infection. Since an etiologic diagnosis of an LRTI in a pediatric patient is problematic, the choice for a particular antibiotic treatment is usually empirical (2). Effective management of bacterial LRTI requires consideration of clinical and practical antibiotic dosing issues and patient compliance, the susceptibility and resistance of possible causative pathogens, and the pharmacokinetic basis for treatment with antimicrobial agents.

TABLE 4. Microorganisms isolated from the lower pharynx before therapy

Organism	No. of patients in group with microorganisms isolated	
	Azithromycin	Erythromycin
H. influenzae	11	8
S. pneumoniae	7	4
M. catarrhalis	4	4
S. pyogenes	1	3
Klebsiella sp.	1	0
S. aureus	0	1

Several antimicrobial agents are available for the treatment of LRTI in childhood. Azithromycin is active against the pathogens responsible for LRTI (*S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *Mycoplasma pneumoniae*, *Coxiella burnettii*, and *Chlamydia pneumoniae*) (7). With the restrictions around infection and colonization status of an organism in mind, it could be observed that the isolated possible pathogens were susceptible to azithromycin and erythromycin, with the expected exception of several *H. influenzae* isolates with intermediate susceptibility or resistance to erythromycin. None of these isolates was associated with a treatment failure or relapse, which makes the clinical relevance of this finding questionable. An important bias of the present study is the use of nasopharyngeal cultures as predictors of the causative microorganisms of the LRTI. We realize the relativity of these findings. However, the principal aim of the study was to investigate the clinical response in an outpatient population with clinically diagnosed lower respiratory infection for which usually no cultures whatsoever would be performed.

Azithromycin penetrates well in the lower respiratory tract (6). The pharmacokinetic characteristics of azithromycin result in less frequent administration and shorter treatment courses compared with erythromycin or beta-lactam regimens, allowing for a shorter treatment. Compliance is influenced not only by the duration of therapy but also by the relatively simple, once-daily dosing of azithromycin. The overall incidence of side effects was greater in the azithromycin-treated patients than in the erythromycin-treated patients, although these differences did not reach statistical significance. Whether these adverse events were related to the study drug cannot be ascertained, since many patients took other concurrent medications. In addition, gastrointestinal symptoms such as vomiting and loose stools are aspecific symptoms of infection in children. The incidence of vomiting was higher in the azithromycin group, although the difference with the erythromycin group was not statistically significant. The episodes of vomiting were mild in all seven cases and took place only once in every patient at the start of therapy, and no patient stopped therapy because of this adverse event. One patient showed transient elevation of alanine transferase. No other possibly drug-related laboratory abnormalities were seen. None of the patients discontinued therapy because of side effects. It is not clear why the proportion of children with side effects receiving erythromycin was lower in the present study compared with data from the literature (3, 4, 10). The open design of the study makes recall bias possible. Patients or their parents might be inclined to report side effects of the new drug more vigorously than of the older one. Moreover, there is great variation in the frequency of reported side effects when the published literature is compared (3, 4, 10). In conclusion, a 3-day course of azithromycin is clinically as effective as a 10-day course of erythromycin in the treatment of acute LRTI in children.

ACKNOWLEDGMENTS

The study was supported by a grant from Pfizer B.V.

We thank the following colleagues for their contribution to the study: A. N. Bosschaart, F. G. A. Versteegh, R. N. Sukhai, J. Verhage, and P. Nevolová.

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