

Comparative Study of Once-Weekly Azithromycin and Once-Daily Amoxicillin Treatments in Prevention of Recurrent Acute Otitis Media in Children

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Received 8 July 1996/Returned for modification 14 August 1996/Accepted 24 September 1996

Continuous chemoprophylaxis is effective in the prevention of new episodes of acute otitis media (AOM) in otitis-prone children, but compliance can be a problem and thus efficacy can be decreased. Intermittent chemoprophylaxis has so far shown conflicting results. Azithromycin, which has a peculiar pharmacokinetics, resulting, even after a single dose, in persistently elevated concentrations in respiratory tissues, could permit a periodic administration with higher compliance. We compared a 6-month course of once-weekly azithromycin (5 or 10 mg/kg of body weight) with that of once-daily amoxicillin (20 mg/kg) in a single-blind, randomized study of prophylaxis for recurrent AOM in 159 children aged 6 months to 5 years with at least three episodes of AOM in the preceding 6 months. In the amoxicillin group, 23 (31.1%) of 74 children developed 29 episodes of AOM, while in the 10-mg/kg azithromycin group, 11 (14.9%) of 74 children experienced 15 episodes. The 5-mg/kg/week azithromycin trial was prematurely interrupted after nine cases, due to the high occurrence rate of AOM (55.5%). During the 6-month prophylaxis period, the proportion of children with middle ear effusion declined similarly in both groups. No substantial modification of the nasopharyngeal flora was noted at the end of prophylaxis in both antimicrobial groups. In the 6-month-postprophylaxis follow-up period, about 40% of children in both groups again developed AOM. Azithromycin at 10 mg/kg once weekly can be regarded as a valid alternative to once-daily low-dose amoxicillin for the prophylaxis of AOM. Although in the present study no microbiological drawback was noted, accurate selection of children eligible for prophylaxis is mandatory to avoid the risk of emergence of resistant strains.

Recurrent acute otitis media (AOM) is common in infants and young children. Because of possible short-term and long-term sequelae, prevention is desirable (2). Among the various approaches which have been proposed (chemoprophylaxis, immunoprophylaxis, surgery, and control of environmental risk factors), chemoprophylaxis has been considered the first option because it is effective in reducing the number of new episodes of AOM and is the most easily practicable (5, 18, 25, 27). Continuous or intermittent schemes of chemoprophylaxis have been suggested. However, whereas continuous prophylactic regimens, including that adopted in our previous study (22), were always effective, intermittent prophylaxis, usually restricted only to periods when upper respiratory tract infections are present, despite being potentially more acceptable, has given contradictory results (3, 12, 21). Continuous prophylaxis is usually favored, even if compliance with this treatment in the routine practice can be a problem and the optimal duration is still to be defined (11).

Recently, the Food and Drug Administration has approved for the treatment of otitis media azithromycin, an azalide antibiotic, structurally related to macrolides but with better activity against *Haemophilus influenzae* and with peculiar pharmacokinetic properties, which allow, even after a single dose, persistently elevated concentrations in respiratory tissues (9, 15, 16, 23). Starting from these premises, it seemed reasonable that a periodic administration of azithromycin could provide the same efficacy of continuous administration of antibiotics traditionally recommended for chemoprophylaxis and, at the

same time, the practical advantages of intermittent administration.

We compared once-weekly azithromycin with once-daily amoxicillin in the prevention of new episodes of AOM in children with a recent history of recurrent AOM.

MATERIALS AND METHODS

Subjects, exclusion criteria, and entry evaluation. The trial was conducted at the Pediatric Department 4 of the University of Milan between November 1992 and March 1996. Children between the ages of 9 months and 5 years who were attending the outpatient clinic were eligible for enrollment. Each child had had at least three documented episodes of AOM in the preceding 6 months with the most recent episode having occurred within 2 to 8 weeks before enrollment. In most cases, referring pediatricians' medical records were relied upon for documentation of prior episodes. Children were required to be free of clinical and otoscopic findings of AOM, but otitis media with effusion (OME) could be present. Excluded from the study were patients who had cleft palate, previous tonsillectomy or adenoidectomy, obstructive adenoid hyperplasia or sleep apnea syndrome, Down syndrome, acquired or congenital immunodeficiency, a gastrointestinal disorder that could diminish antibiotic absorption, or a history of documented allergic reactions to any of the drugs tested. Also excluded were patients who had undergone surgical placement of tympanostomy tubes or had chronically ruptured tympanic membrane. The study was approved by the Ethical Committee of the University of Milan. Written informed consent was obtained from parents or guardians of the child.

Assignment to treatment groups. At entry, each patient was assigned randomly (by a random allocation scheme developed before the start of the study) to one of three study groups: (i) amoxicillin, 20 mg/kg of body weight per day; (ii) azithromycin, 10 mg/kg in a single dose followed by 5 mg/kg/week; and (iii) azithromycin, 10 mg/kg/week. Amoxicillin was given once daily at bedtime in syrup form while azithromycin suspension was administered once weekly, on the same day of the week. All the patients were treated for 6 months. No placebo group was included, because we considered it unethical, on the basis of our previous study, to keep without a prophylactic treatment children at risk of recurrences (22).

Management during study period. Patients were examined at entry and subsequently at intervals of 4 to 6 weeks and whenever they developed symptoms of

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upper respiratory tract illness or symptoms suggesting AOM. At each visit, an interval history was obtained, and pneumatic otoscopy and tympanometry were performed. Pneumatic otoscopy was carried out in each case by the same examiner (P.M.), blinded about the drug treatment, using a standard otoscope (Welch Allyn model 20200). Tympanograms were obtained with an electroacoustic bridge (Amplifon; model Amplaid 770). To ensure investigator blinding, the study drug was dispensed by a nurse and the parent (or guardian) of each patient was instructed not to discuss the frequency of dosing with the physician.

The diagnosis of AOM was based on the presence of any combination of fever, otalgia, and irritability and on the presence of hyperemia or opacity accompanied by fullness, bulging, or immobility of the tympanic membrane; tympanometry was performed to assist in defining the presence of middle ear effusion in doubtful cases. The diagnostic criteria for OME consisted of the presence of impaired mobility; opacification and either bulging or retraction of the tympanic membrane, associated with a flat, type B tympanogram; and the absence of general or local signs and symptoms of acute infection.

Children were given written instructions about the use of salt water nasal drops in order to relieve nasal congestion if an upper respiratory tract infection developed after enrollment. No other cold remedies (including systemic or local decongestant and antihistamines) were allowed. Whenever AOM was diagnosed, prophylaxis was discontinued and treatment with amoxicillin plus clavulanic acid (50 mg of amoxicillin per kg/day) was prescribed for 10 days. Bilateral involvement was counted as a single episode. After treatment, if acute signs had subsided, prophylaxis with the original drug was resumed. If acute signs persisted, the study protocol called for tympanocentesis to be performed and another antimicrobial drug to be administered, based on the sensitivity of the isolated pathogen. Tympanocentesis was contemplated only for children with persistent findings of AOM, because of the invasiveness of the procedure and to avoid any possible influence on the course of middle-ear effusion. If another infectious disease requiring antibiotic treatment occurred, prophylaxis was stopped, the more appropriate treatment was instituted, and following recovery, prophylaxis was reinstated. A child was discharged from the study if two episodes of AOM occurred within an 8-week period. Children attending a day-care center at the time of enrollment continued to do so throughout the study period.

Biochemical and microbiology controls. At entry into the study and at the end of the prophylactic period, a blood sample was taken from each patient for determination of hematologic, renal, and hepatic parameters to detect drug toxicity and nasopharyngeal cultures were performed, with a Mini-Culturette (Becton-Dickinson, Cockeysville, Md.) placed 1 to 1.5 in. (ca. 3 to 4 cm) into the nasopharynx. Specimens were processed in the same laboratory within 2 h of procurement, in order to detect the presence of *Streptococcus pneumoniae*, *H. influenzae*, *Moraxella catarrhalis*, and *Streptococcus pyogenes*. Susceptibilities were determined by Kirby-Bauer disc diffusion; all *H. influenzae* and *M. catarrhalis* isolates were to be tested for β -lactamase production with a chromogenic cephalosporin disc method. *S. pneumoniae* isolates were screened for penicillin resistance with an oxacillin disc test, and if appropriate, MICs were assessed by microdilution.

Compliance and parents' satisfaction evaluation. Compliance with the study regimen was encouraged by asking parents to affix a written reminder of the protocol to the refrigerator door. Parents were also asked to bring the medication bottles with them at follow-up visits, and compliance was evaluated on the basis of the amount of drug remaining in the bottle. Failure to administer three or more doses of amoxicillin or one dose of azithromycin in a 4-week period was considered poor compliance, but this was not a reason for interrupting prophylaxis. After 3 months of prophylaxis and again at the end of the prophylactic period, parents were asked about the rate of satisfaction with the current prophylactic regimen: satisfaction was rated as very satisfied, satisfied, or unsatisfied.

Analysis. The occurrence rate of AOM was calculated as episodes per patient-month during the study period. The finding of OME in the same ear on two consecutive examinations was considered indicative of the persistence of OME in this ear during the intervening period. The same criterion was adopted for ears without OME: when OME was present on one examination and absent in the next, or vice versa, effusion was considered to have been present during half of the interval, that is, 2 to 3 weeks (in the case of fractions, the value in weeks of effusion was rounded to the nearest unit).

Postprophylaxis period. After the 6-month prophylactic period, children were to be monitored for the next 6 months. Clinical and otoscopic controls were the same as in the study period. No laboratory or microbiology controls were done. Occurrence rate of AOM was evaluated as in the prophylactic period.

Statistical methods. Statistical comparison was performed by SPSS for Windows, release 6 (SPSS, Bologna, Italy) with either nonparametric tests or exact tests. A level of $P < 0.05$ was chosen to reflect statistical significance. Categorical data were compared by chi-square test with Yates' correction for fourfold tables, unless the sample was too small, in which case Fisher's exact test was used. A logistic multivariate modeling was used to investigate whether, in addition to the method of treatment, age, sex, season at entry, or day-care attendance influenced outcome, and whether there were interactions between any of these latter subject characteristics and the method of treatment.

TABLE 1. Occurrence of AOM during 6-month study period

Type of value	Amoxicillin (20 mg/kg/day) (<i>n</i> = 74)	Azithromycin (10 mg/kg/wk) (<i>n</i> = 74)
No. of children with AOM	23 (31.1%)	11 (14.9%) ^a
No. of episodes of AOM	29	15
Mean no. of episodes per child-month	0.06	0.03
Mean no. of episodes per patient	0.39	0.20

^a $P < 0.05$ versus amoxicillin.

RESULTS

Prophylaxis period. (i) Subject characteristics. A total of 159 children entered the study and were randomized to receive amoxicillin (*n* = 75); azithromycin, 5 mg/kg/week (*n* = 9); or azithromycin, 10 mg/kg/week (*n* = 75). One child in the amoxicillin group and one child in the 10-mg/kg/week azithromycin group refused to return to follow-up visits after 2 months and were therefore not considered in the study. The number of children enrolled in the 5-mg/kg/week azithromycin group is lower than the other two groups because the inclusion was prematurely interrupted because of the high occurrence rate of AOM in this group, similar to that of the placebo group in our previous study: overall, 5 of 9 (55.5%) of the children had new episodes of AOM and 4 of 9 (44.4%) had two episodes of AOM within the first 8-week period and were thus discharged from the study and no longer analyzed for duration of effusion or occurrence of AOM in relation to epidemiologic factors. Their data are not reported in the tables. The interruption of the low-dose group of azithromycin treatment was not disclosed to the blinded investigator (P.M.). From the moment of interruption, children were randomized to receive only amoxicillin or 10-mg/kg/week azithromycin.

Children enrolled in the amoxicillin and in the higher-dose azithromycin group were comparable for age (mean age, 35.8 versus 36.8 months), sex, season of entry (October to March, 77 versus 81%), number of previous AOM episodes (three episodes, 66.2 versus 71.6%; four to six episodes, 33.8 versus 28.4%), initial ear status (bilateral or unilateral OME, 90.5 versus 93.2%), number of siblings, and day-care attendance (5 days/week, 6 to 8 h/day). Forty-five (60.8%) children in the amoxicillin group and 38 (51.4%) in the azithromycin group were younger than 2 years of age.

(ii) Rates of AOM. In the amoxicillin group, 23 of 74 (31.1%) children developed 29 episodes of AOM (17 children had one episode and 6 children had two episodes); in the azithromycin (10 mg/kg/week) group, 11 of 74 children (14.9%) experienced 15 episodes of AOM (seven had one episode and four had two episodes) (Table 1). The difference in the proportions of children who developed AOM is statistically significant ($P = 0.03$; difference, 16%; 95% confidence interval, 2.92 to 29.5%). In one patient in each group, prophylaxis was interrupted (in the child in the amoxicillin group after 4 months and in that given azithromycin after 3 months) because of failure despite good compliance. All the other children completed the entire period of prophylaxis. No child underwent tympanocentesis because all the children with recurrent AOM resolved on treatment with amoxicillin plus clavulanic acid.

Irrespective of the season at entry and treatment group, a substantial proportion of all episodes of AOM (18 of 44, 40.9%) occurred between April and September. Children given amoxicillin developed 123 episodes of apparently viral

TABLE 2. Occurrence of AOM during prophylaxis in relation to epidemiologic factors

Patient characteristic	No. with characteristic/total no. (%) for group	
	Amoxicillin (20 mg/kg/day)	Azithromycin (10 mg/kg/wk)
Age		
9 mo–2 yr	15/45 (33.3)	7/38 (18.4)
>2–5 yr	8/29 (27.5)	4/36 (11.1)
Sex		
Male	11/44 (25.0)	7/41 (17.0)
Female	11/30 (40.0)	5/31 (12.1) ^a
Season at entry		
October–March	19/57 (33.3)	9/60 (15.0) ^a
April–September	4/17 (23.5)	2/14 (14.2)
Day-care attendance		
Yes	13/44 (29.5)	10/53 (18.9)
No	10/30 (33.3)	1/21 (4.8) ^a

^a $P < 0.05$ versus amoxicillin.

upper respiratory tract infection (mean number of episodes per child, 1.66) while children given azithromycin at 10 mg/kg/week developed 109 episodes of upper respiratory tract infection (mean number of episodes per child, 1.47). Two children in each group developed acute streptococcal pharyngitis and were treated accordingly; no serious bacterial infections were reported.

Table 2 shows data on the occurrence of AOM in the various epidemiologic subgroups. Consistently across subgroups, the rate of occurrence of AOM was lower in children receiving azithromycin at 10 mg/kg/week than in patients given amoxicillin; the difference reaches statistical significance only in certain of the subgroups, in particular in children who were enrolled in the autumn-winter season and in children not attending day care. The stepwise logistic analysis demonstrated that no statistically significant interactions were present among any of the subject characteristics and the method of treatment.

(iii) **OME.** By the end of the 6-month period, the proportion of children with OME had declined in both groups without any significant difference: 19 of 73 (27.0%) children given amoxicillin had bilateral OME, 10 (13.5%) had unilateral OME, and 44 (59.5%) were free of effusion. In the 10-mg/kg/week azithromycin group, 26 of 73 (36.4%) still had bilateral OME, 11 (14.8%) had unilateral OME, and 36 (48.6%) were free of middle ear effusion. The cumulative duration of effusion (either bilateral or unilateral), expressed as percentage of total patient-weeks, was not different in the two groups: 60.1% in the amoxicillin group and 58.9% in the azithromycin group.

(iv) **Compliance and parents' satisfaction.** A total of 93.4% of amoxicillin doses and 100% of azithromycin doses were correctly administered. All parents reported satisfaction with the prophylactic regimen: however, the proportion of "very satisfied" was significantly higher when giving azithromycin in comparison with those giving amoxicillin (51 of 74, 68.9%, versus 29 of 74, 39.2%; $P < 0.001$).

(v) **Microbiology and tolerability.** Both drugs were safe and well tolerated. No laboratory or clinical toxic side effects were demonstrated. Moreover, in neither of the two prophylactic regimens was any remarkable modification of the nasopharyngeal flora demonstrated, as regards both the prevalence of the bacteria and their susceptibility to betalactams and macrolides: the few children who, at entry, harbored respiratory pathogens had negative nasopharyngeal cultures at the end of prophylaxis,

TABLE 3. Nasopharyngeal colonization according to prophylactic regimen

Drug and baseline nasopharyngeal culture	End-of-prophylaxis nasopharyngeal culture	
	Negative ^a	Positive ^a
Amoxicillin		
Negative ($n = 66$) (89.2%)	60	5 ^b
Positive ($n = 8^c$) (10.8%)	8	0
Azithromycin		
Negative ($n = 67$) (90.5%)	66	1 ^d
Positive ($n = 7^e$) (9.5%)	7	0

^a Negative or positive for *S. pneumoniae*, *H. influenzae*, *S. pyogenes*, or *M. catarrhalis*. Only resistance to beta-lactams and azithromycin is shown.

^b *S. pyogenes*, 3; *H. influenzae*, 2 (1 resistant to azithromycin).

^c *S. pneumoniae*, 3; *S. pyogenes*, 2; *H. influenzae*, 3.

^d *S. pyogenes*.

^e *S. pneumoniae*, 3; *H. influenzae*, 4.

while among those children not colonized at the beginning of prophylaxis, only 6 (4.7%) had positive nasopharyngeal cultures by the end of the treatment (Table 3). Only one strain of *H. influenzae*, isolated in a child treated with amoxicillin, was resistant to azithromycin. *S. pneumoniae* showed no resistance to penicillin. No strain of *H. influenzae* was producing β -lactamases.

Postprophylaxis period. Seventy children in the amoxicillin group and 69 in the 10-mg/kg/week azithromycin group completed the 6-month postprophylaxis follow-up period. In the group given amoxicillin, 30 of 70 children (40.5%) developed 46 episodes of AOM (17 children had one episode, 10 had two episodes, and 3 had three episodes); in the azithromycin group, 27 of 69 children (39.1%) developed 42 episodes (18 children had one episode, 5 had two episodes, 2 had three episodes, and 2 had four episodes). In both groups, each child experienced 0.10 episode per child-month. No statistical difference was noted between the two treatment groups as regards epidemiologic subgroups (sex, presence of OME at the end of prophylaxis, season, day-care attendance). Of the subject characteristics other than method of treatment, only age influenced outcome: 21 of 26 children (80.7%) who had stopped prophylaxis at younger than 2 years of age had recurrences of AOM, compared with 36 of 113 children (31.8%) whose prophylactic treatment ended after 2 years of age (relative risk, 6.04; 95% confidence interval, 2.42, 15.08).

DISCUSSION

Chemoprophylaxis is the most feasible and one of the most efficacious medical approaches to the prevention of recurrent AOM. All the other interventions are either less efficacious or less practicable or have more adverse effects. Immunoprophylaxis, either passive or active, has so far had a limited role (13). Control of environmental factors (reduction of passive smoking exposure, of use of pacifiers, and of time spent in day care) is frequently impracticable, while breast-feeding, which can prevent recurrences in the first year of life, is not always possible (6, 8). Moreover, surgical interventions such as myringotomy with tympanostomy tube placement are burdened by well-documented potential risks and costs while the value of adenoidectomy is still debated (4, 20).

Continuous or intermittent regimens of chemoprophylaxis have been suggested. Amoxicillin or sulfonamides administered continuously have been the drugs and scheme of choice for years. However, compliance with a continuous regimen can be difficult in the routine clinical practice, especially when

regarding an urban population of children not included in a formal prospective study (11).

Studies on intermittent prophylaxis during upper respiratory tract infections have so far given conflicting results (3, 12, 21). Moreover, its practicability is questionable because during upper respiratory tract infections it is difficult to define the exact time to begin the antimicrobial treatment, as cold symptoms can be very mild or transient and can be initially difficult to ascertain for most of the parents. Moreover, cold symptoms can persist for weeks or months during the winter season; thus, this intermittent prophylaxis can actually become very similar to a continuous one.

A dose of 5 mg of azithromycin per kg once weekly is not enough to effectively prevent AOM. In contrast, when given at the dose of 10 mg/kg once weekly, azithromycin is statistically superior to continuous amoxicillin in preventing new episodes of AOM in children with a recent history of recurrent AOM, even if from a clinical point of view the difference has only a marginal importance. The once-weekly regimen, however, is preferred and thus assures a greater compliance in everyday practice, when continuous monitoring is lacking. The good compliance in amoxicillin patients was undoubtedly favored by the design of the formal prospective study.

It is not clear why azithromycin is superior to amoxicillin in the prevention of AOM. One hypothesis could be the better penetration of azithromycin in respiratory tissues and thus the possibility of eliminating or reducing the presence of those bacteria (such as noncapsulated, nontypeable *H. influenzae*) which can reside intracellularly and therefore can become protected from the defense mechanisms of the host, resulting in a chronic carrier state (26).

Chemoprophylaxis had no substantial effect on the persistence of middle ear effusion: by the end of the treatment period the proportion of children with OME was similar, independently from the drug, to that of the placebo group in our previous study (22).

In the 6-month postprophylaxis period, almost 40% of the children in both groups had new episodes of AOM. However, the recurrence rate was much less than that demonstrated before prophylaxis: only 0.10 episode per child-month in both groups. This is probably more attributable to the spontaneous reduced frequency of AOM over time than to a long-term effect of antibiotic administration. However, children who interrupted prophylaxis before reaching 2 years of age were at significantly higher risk of having recurrences: this raises the problem of a longer duration of prophylaxis when it is begun in very young children.

The wide utilization of chemoprophylaxis in children has been recently severely questioned because of its possible role in the emergence of resistant strains of bacteria (10, 19). Prophylaxis has been associated with secondary infections in surgical patients and with colonization with resistant strains of *S. pneumoniae* in children attending day-care centers (1, 17, 24). However, in our study as well in the other two studies which have monitored the microecology of the nasopharynx during chemoprophylaxis for recurrent AOM, no direct association between prophylaxis administration and emergence of resistant strains was shown (3, 7). In our study, only a small proportion of children harbored bacteria at the beginning of the prophylactic regimen: this can be explained by the fact that in most cases the last episode of AOM had presented within the previous 4 weeks and thus had been recently treated with a full course of antibiotics. The absence of selection of resistant strains was also favored by the low prevalence in our patients of penicillin resistance of *S. pneumoniae* and of β -lactamase

production of *H. influenzae*, which is consistent with what is currently found in Italy, even in adults (14).

Anyhow, in order to limit the risk of microbiologic problems and to maximize the efficacy of chemoprophylaxis, a more strict selection of children is desirable. Firstly, only children less than 2 years of age who are at higher risk of recurrent AOM and in whom chemoprophylaxis has been demonstrated to be more effective should be considered eligible. Secondly, only children with at least three documented and adequately treated episodes of AOM within the prior 6 months should be given prophylaxis, sparing those children with a less frequent recurrence rate, such as those with four episodes in 12 months or five total. The third criterion of selection could be the demonstrated impossibility of controlling environmental risk factors (such as high level of home crowding or high number of siblings).

When choosing prophylaxis, azithromycin at 10 mg/kg once weekly can be actually regarded as a valid alternative to continuous amoxicillin. Azithromycin could be suggested as a first choice in those children for whom compliance with a continuous long-term treatment could be problematic, in children allergic to beta-lactams, or when bacteria resistant to amoxicillin and sensitive to new macrolides are highly prevalent in the population.

ACKNOWLEDGMENT

This work was supported in part by Pfizer Italiana S.p.A., Rome, Italy.

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