

NOTES

Comparative Efficacy and Safety of 3-Day Azithromycin and 10-Day Penicillin V Treatment of Group A Beta-Hemolytic Streptococcal Pharyngitis in Children

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The efficacy and safety of a 3-day course of azithromycin oral suspension (10 mg/kg of body weight once daily) were compared with those of penicillin V (50,000 U/kg/day in two divided doses) in children aged 3 to 12 years for the treatment of symptomatic pharyngitis caused by the group A beta-hemolytic streptococcus (GABHS). For the 154 evaluable patients, the original infecting strain of GABHS was eliminated at the end of follow-up (34 to 36 days after treatment started) from 67 (85.8%) of 78 penicillin-treated patients and 41 (53.9%) of 76 azithromycin-treated patients ($P < 0.0001$). Overall clinical success was achieved in 71 (91.0%) of 78 penicillin V-treated patients and 57 (75.0%) of 76 azithromycin-treated patients ($P < 0.05$). Potential drug-related adverse events were reported for 5.5 and 8.6% of the penicillin V- and azithromycin-treated patients, respectively ($P = 0.6$). In the present study, a once-daily (10 mg/kg), 3-day oral regimen of azithromycin was as safe as a 10-day course of penicillin but did not represent an effective alternative to penicillin for the treatment of GABHS pharyngitis, even for those children with azithromycin-susceptible strains.

The group A beta-hemolytic streptococcus (GABHS) remains an important cause of acute pharyngitis, especially among school-aged children. Penicillin continues to be the drug of choice for GABHS pharyngitis (6) despite the increasing number of reported treatment failures (10). The reasons for such failures are unclear but may include poor patient compliance (10), inactivation of penicillin by the β -lactamases produced by throat commensals (4), the carrier state (12), or possibly GABHS tolerance to penicillin (11).

This issue has stimulated much interest in the development of a number of alternatives to penicillin for the management of pediatric GABHS pharyngitis. One aim of these investigations has been to identify agents with simpler dosing regimens and shorter treatment durations in hopes of enhancing patient compliance and therapeutic success (1, 17, 21). Several studies have confirmed results from the 1950s that showed that shortened courses of oral penicillin produce an inferior bacteriologic eradication rate compared with that of the traditional 10-day course (2, 8, 18).

As a result of its pharmacokinetic profile, azithromycin is unique among these alternative agents in allowing once-daily dosing and a shorter duration of treatment (7). As was previously established in adults, the sustained concentrations of azithromycin in plasma after oral dosing of pediatric patients, coupled with the drug's prolonged tissue half-life, suggest that comparatively short azithromycin treatment regimens should be effective for the management of GABHS pharyngitis in pediatric patients (14).

Early clinical trials have indicated that a single 10-mg/kg of

body weight dose of azithromycin once daily for 3 days is equal in efficacy to 10 days of treatment with penicillin V for pediatric patients infected with such a clinical entity (9). In our country, azithromycin has recently been licensed for use in adults and children with upper or lower respiratory tract infections (including GABHS pharyngitis) or skin and chlamydial urogenital infections and is to be administered on a 3-day, once-daily dosing (total dose, 30 mg/kg) schedule. The clinical study described in this report was designed to evaluate the efficacy and safety of a 3-day azithromycin regimen and to compare it with a penicillin V regimen for the treatment of pediatric patients with acute pharyngitis and a positive throat culture for GABHS.

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Between February 1993 and October 1994, children aged 3 to 12 years from the acute care clinic of the Institute of Pediatrics, La Sapienza University of Rome, were enrolled in this study if they had one or more signs (e.g., tonsillopharyngeal exudate, cervical lymphadenitis, scarlatiniform rash, and strawberry tongue) and one or more symptoms (e.g., fever, sore throat, difficulty in swallowing, abdominal pain, and headache) compatible with a presumptive diagnosis of GABHS pharyngitis. GABHS infection was initially presumed on the basis of a positive rapid streptococcal antigen test (Testpack Strep A; Abbott Laboratories); infection was subsequently confirmed by throat culture. The details of the culture methods have been presented elsewhere (5).

The main excluding criteria for prospective study participants were known hypersensitivity to macrolide or beta-lactam antibiotics, oral or parenteral treatment with any antibiotic within 7 days before enrollment, treatment with long-acting

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penicillin injections within the preceding 6 weeks, evidence or history of significant hepatic or renal abnormalities, and malabsorption or other conditions affecting drug absorption. Patients enrolled in the study were assigned according to a computer-generated randomization schedule to receive oral treatment with either azithromycin or penicillin V. The daily dose of azithromycin (10 mg/kg) was administered as an oral suspension (200 mg/5 ml) taken as a single dose for 3 days. Penicillin V (phenoxymethyl penicillin) was given at a total daily dose of 50,000 U/kg divided into two equal doses for 10 days. The doses were administered 1 h before or 2 h after meals. Compliance was assessed both with patient diary card and on the basis of the calculated amount of drug consumed; informed consent from a parent or guardian was required before study entry. All patients were scheduled for clinical evaluations and throat swabs at baseline (visit 1) and at day 4 to 5 (visit 2), day 12 to 14 (visit 3), and day 34 to 36 (visit 4) after the start of antibiotic therapy, but they were told to return whenever signs and symptoms suggestive of GABHS infection recurred during the 5-week follow-up period. Testing of all pretreatment GABHS cultures and any repeat GABHS cultures for susceptibility to azithromycin (15- μ g disk) and penicillin (10-U disk) was performed by agar disk diffusion. Susceptibility to either study drug was defined with the following breakpoint criteria (15): resistance to azithromycin, <14-mm-diameter inhibition zone, and resistance to penicillin, <20-mm-diameter inhibition zone. *Staphylococcus aureus* ATCC 25923 was used as a control. All isolates were serologically typed by T-agglutination patterns as previously described (13). Laboratory testing (hematology, blood chemistry, and complete urinalysis) was performed at visits 1 and 3. Blood specimens for paired anti-streptolysin O and anti-DNase B antibody titers were obtained at visits 1 and 4 and were later analyzed as previously described (16). Changes in antibody titers (acute to convalescent) were determined as the difference in logs (Δ log). A significant change in antibody titers was defined as a rise equal to or greater than 0.2 log (16). Clinical and bacteriologic outcomes were assessed at visits 3 and 4. Clinical efficacy was defined as success (resolution or substantial improvement of all pretreatment signs and symptoms), failure (pretreatment signs and symptoms not improved or worsened at visit 3), and recurrence (resolution or substantial improvement of signs and symptoms at visit 3 with subsequent deterioration or reappearance at any time through visit 4). Bacteriologic efficacy was defined as elimination (absence of GABHS in the follow-up throat cultures), failure (presence of the original T type in the throat cultures obtained at visit 3 regardless of the number of colonies per plate), recurrence (eradication of pretreatment GABHS at visit 3 with recurrence of the baseline T type at any time through visit 4 regardless of the number of colonies per plate), and reinfection (eradication of the pretreatment T type from all subsequent throat cultures with the isolation of a different GABHS T type at any time through visit 4).

At the follow-up visits, if the cultures yielded more than 10 colonies per plate, the patient was retreated with a nonstudy antibiotic agent and discontinued from further study. If the cultures yielded fewer than 10 colonies and the patient was asymptomatic, no additional treatment was given and the patient was followed up per protocol. Safety analysis was performed for all patients who had received at least one dose of the study drug.

A total of 183 patients were enrolled into the study. GABHS was isolated from 179 patients. No isolates were resistant to penicillin, whereas 31 (17.3%) of the 179 isolates from admission cultures were resistant to azithromycin. Of the 31 isolates, 28 (90.3%) belonged to the T-4 serotype and 3 belonged to the

TABLE 1. Demographic characteristics of evaluable patients in the two treatment groups

| Characteristic | No. (%) of patients ^a | |
|-------------------------------------|----------------------------------|--------------------------------|
| | Azithromycin group (n = 76) | Penicillin V group (n = 78) |
| Sex | | |
| Male | 36 (47.3) | 39 (50.0) |
| Female | 40 (52.6) | 39 (50.0) |
| Symptoms | | |
| Sore throat | 76 (100) | 78 (100) |
| Difficulty in swallowing | 55 (72.3) | 59 (75.6) |
| Headache | 32 (42.1) | 35 (44.8) |
| Abdominal pain | 21 (27.6) | 24 (30.7) |
| Signs | | |
| Fever ($\geq 38^{\circ}\text{C}$) | 69 (90.7) | 72 (92.3) |
| Erythema pharynx | 76 (100) | 78 (100) |
| Tonsillar or pharyngeal exudate | 50 (65.7) | 54 (69.2) |
| Lymph node tenderness | 66 (86.8) | 67 (85.8) |
| Scarlet fever | 24 (32.8) | 22 (28.2) |

^a The mean patient ages were 6.7 years for the azithromycin group and 6.9 years for the penicillin V group (the range for both groups was 3 to 12 years).

T-1 serotype. None of the pretreatment isolates sensitive to azithromycin became resistant during treatment or follow-up.

Seventy-six (81.7%) of 93 azithromycin-treated patients and 78 (86.6%) of 90 penicillin V-treated patients met the inclusion criteria for efficacy evaluation. In the azithromycin group, three patients were excluded from the efficacy analysis for the following reasons: negative pretreatment culture ($n = 2$) and lack of follow-up examination ($n = 1$). An additional 14 azithromycin-treated patients were excluded from the efficacy analysis because their isolates of GABHS upon enrollment were resistant to this drug. Of these 14 patients, at visit 2, 10 had pretreatment signs and symptoms that had persisted or worsened as well as throat cultures strongly (>100 CFU of GABHS) positive for the original infecting organism, 1 had a bacteriologic and clinical failure, and 1 had a bacteriologic and clinical recurrence. The remaining two patients achieved clinical success and bacteriologic elimination at visit 4. In the penicillin V group, 12 patients were disqualified because of negative pretreatment culture ($n = 2$), noncompliance ($n = 6$), incomplete follow-up ($n = 3$), and use of a nonstudy antimicrobial agent ($n = 1$).

As can be seen from Table 1, the evaluable patients in the two treatment groups were similar with respect to age, gender, and clinical findings at the time of the initial visit. All 154 evaluable patients had throat cultures strongly positive for GABHS infection (e.g., 87.6% of these patients grew ≥ 100 CFU of GABHS and the remainder grew >50 but <100 CFU).

Clinical and bacteriologic outcomes are summarized in Table 2. Significantly more ($P < 0.05$) penicillin V-treated patients (91.0% [71 of 78]) than azithromycin-treated patients (75.0% [57 of 76]) achieved clinical success at visit 4. Likewise, a significantly ($P < 0.0001$) greater proportion of patients in the penicillin V group (83.3% [65 of 78]) than in the azithromycin group (50.0% [38 of 76]) achieved bacteriologic elimination at visit 4. The combined bacteriologic failure-plus-recurrence rate was 14.1% (11 of 78) for the penicillin V treatment group and 46.0% (35 of 76) for the azithromycin treatment group ($P < 0.0001$). Patients were analyzed for the occurrence of reinfection during follow-up, and there were no statistically ($P = 0.9$) significant differences between the two treatment groups (penicillin V, 2 of 78, and azithromycin, 3 of

TABLE 2. Clinical and bacteriologic responses for the efficacy populations

| Response by treatment group ^a | No. responding/total no. | | |
|--|--------------------------|--------------------|----------------------|
| | Visit 3 | Visit 4 | Overall ^b |
| Azithromycin (n = 76) | | | |
| Clinical efficacy | | | |
| Success | 65/76 | 57/65 | 57/76 |
| Failure | 11/76 | | 19/76 |
| Recurrence | | 8/65 | |
| Bacteriologic efficacy | | | |
| Elimination | 51/76 | 38/51 | 38/76 |
| Failure | 24/76 ^c | | 35/76 |
| Recurrence | | 11/51 ^d | |
| Reinfection | 1/76 | 2/51 | 3/76 |
| Penicillin (n = 78) | | | |
| Clinical efficacy | | | |
| Success | 73/78 | 71/73 | 71/78 ^e |
| Failure | 5/78 | | 7/78 |
| Recurrence | | 2/73 | |
| Bacteriologic efficacy | | | |
| Elimination | 71/78 | 65/71 | 65/78 ^f |
| Failure | 7/78 ^d | | 11/78 |
| Recurrence | | 4/71 ^d | |
| Reinfection | 0/78 | 2/71 | 2/78 |

^a No patients in either treatment group had throat cultures positive for GABHS at visit 2.

^b Figures for failures include recurrences.

^c Among these 24 patients, 6 had light (<10 CFU/plate) growth cultures. All these 6 patients had subsequent cultures with heavier growth.

^d All these patients had cultures yielding >10 CFU/plate.

^e $P < 0.05$ for penicillin V versus azithromycin (chi-square test).

^f $P < 0.0001$ for penicillin V versus azithromycin (chi-square test).

76). None of these five patients had clinical failure or clinical recurrence. Seroconversion rates for the two treatment groups were similar. Significant increases in anti-streptolysin O and/or anti-DNase antibody titers were seen for 64.4% (49 of 76) of azithromycin-treated patients and 66.6% (52 of 78) of penicillin V-treated patients.

All 183 patients enrolled in the study were included in the safety analyses. No serious adverse events were observed in either group. Adverse experiences were reported in 8 (5, diarrhea; 1, abdominal pain; 1, nausea; and 1, headache and dizziness [8.6%]) of 93 azithromycin-treated patients and 5 (2, vomiting; 2, diarrhea; and 1, skin rash [5.5%]) of 90 penicillin V-treated patients ($P = 0.6$). None of the patients showed significant laboratory abnormalities.

The best available data on the comparative evaluation of a 3-day course of azithromycin and a 10-day course of penicillin V for the treatment of GABHS pharyngitis in children are those of Hamill (9), who found no significant differences in the clinical and bacteriologic outcomes for the two treated groups throughout the 31-day follow-up period after the start of treatment. In our study, in contrast, azithromycin appeared significantly inferior to penicillin V in eliminating the initial infecting T type of GABHS from those patients with susceptible strains regardless of whether the follow-up period considered for both groups was at day 12 to 14 or day 34 to 36 after treatment started. Overall, the penicillin V-treated patients had significantly more satisfactory clinical responses than the azithromycin-treated patients. That a 3-day course of azithromycin does not represent an equal or more effective alternative to a 10-day course of penicillin V can be inferred from Still's data (19, 21), which showed that a 5-day (total dose, 30 mg/kg) regimen of azithromycin appeared equal in bacteriologic effi-

cacy to a 10-day regimen of penicillin V at the end of treatment; however, compared with penicillin V-treated patients, a significantly higher number of azithromycin-treated patients had bacteriologic recurrences with homologous strains during the 3-week posttreatment follow-up period, suggesting that the dose used may have been inadequate. In a subsequent comparative trial, Still (20, 21) reported that azithromycin administered at a higher total dose (60 mg/kg) for 5 days was statistically superior to penicillin V in bacteriologic and clinical responses at both days 14 and 30 after the start of treatment. The emerging therapeutic efficacy of a 5-day course of azithromycin at a higher total dose for children with GABHS pharyngitis seems worthy of consideration, but trends in azithromycin-resistant populations of GABHS should be periodically monitored to assure that the treatment of GABHS disease with azithromycin is effective.

At the time our comparative trial began, the most recent available data on the macrolide resistance of GABHS strains encountered in our country were those reported by Borzani et al. in 1989 (3). These authors found that the erythromycin resistance rates of their GABHS clinical isolates were 1.6% in 1985 and 6.0% in 1986 to 1987 (3). Because clinical microbiology laboratories do not usually assay the susceptibility of GABHS isolates to antibiotics, the unexpected 17.3% azithromycin resistance rate for our GABHS isolates from admission cultures mandates constant monitoring of the antibiotic susceptibility of GABHS isolates.

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