Effect of Telithromycin and Azithromycin on Nasopharyngeal Bacterial Flora in Patients With Acute Maxillary Sinusitis

Itzhak Brook, MD, MSc; Jeffrey N. Hausfeld, MD, MBA

Objective: To explore the efficacy of the ketolide telithromycin compared with azithromycin in eradicating S pneumoniae from the nasopharynx of adults with acute maxillary sinusitis. The growing resistance of Streptococcus pneumoniae to penicillin and macrolides brought about the development of a new class of antibiotics—the ketolides—that are effective against resistant pneumococci.

Setting: Otolaryngology clinic.

Patients: One-hundred five patients with acute maxillary sinusitis.

Interventions: Nasopharyngeal cultures were obtained before therapy and 10 to 12 days after initiation of treatment. Fifty-nine patients were treated with 500 mg of azithromycin daily for 3 days and 46 were treated with 800 mg of telithromycin daily for 5 days.

Results: Sixty-seven potential pathogens were recovered prior to initiation of therapy in 57 patients, 32 treated with telithromycin and 25 treated with azithromycin: S pneumoniae (31 isolates), Haemophilus influenzae (non-type b) (13), Staphylococcus aureus (8), Streptococcus pyogenes (8), and Moraxella catarrhalis (7). The distribution of the pathogens was similar in both groups. The number of S pneumoniae isolates in the azithromycin group was reduced following treatment from 14 to 8 (43% reduction), and 5 of these 8 isolates were resistant to azithromycin. In contrast, the number of S pneumoniae isolates in the telithromycin group was reduced following treatment from 17 to 1 (94% reduction) (P<.01). This isolate was susceptible to azithromycin and telithromycin. No differences were noted in the eradication rate of all of the other potential pathogens, which were all susceptible to both azithromycin and telithromycin. Development of resistance to the antimicrobial agents used (defined as increase in the minimal inhibitory concentration by at least 2 tubes) was found only in 5 isolates (4 S pneumoniae and 1 H influenzae) recovered only from patients who received azithromycin (P<.05).

Conclusion: These data illustrate the superiority of telithromycin to azithromycin in the eradication of S pneumoniae from the nasopharynx.


The growing resistance to antimicrobial agents of all respiratory tract bacterial pathogens has made the treatment of bacterial sinusitis more difficult. Failure of antimicrobials to clear the infection can be due to persistence of the pathogen(s) because of inadequate pharmacokinetic and pharmacodynamic qualities of the antimicrobials and the development of resistance to the antimicrobial used.1,2

The macrolide antibiotics are generally effective against streptococci and have been used for the treatment of respiratory tract infections because of their spectrum of activity against the major pathogens. Historically, they are considered alternative to penicillin in cases of allergy or resistance to β-lactams.3 However, macrolide resistance in both Streptococcus pneumoniae and Streptococcus pyogenes has been increasingly detected across the world.4 It is especially common among penicillin-resistant pneumococci and has been detected at a variable rate in different epidemiological settings, raising the question of the efficacy of these agents in the treatment of streptococcal infections.5 Cross-resistance is especially of great concern in macrolides, since resistance to 1 member of this group may result in resistance not only to other macrolides but also to lincosamides and group B streptogramins (so-called MLSβ resistance).6

Telithromycin is the first ketolide antibacterial approved for the treatment of community-acquired respiratory tract infections. Telithromycin is highly active in vitro against common community-acquired respiratory tract infection pathogens,7 including S pneumoniae resistant to penicillin and/or erythromycin,8 and atypi-
cal/intracellular pathogens. The targeted antibacterial spectrum of telithromycin is complemented by a low potential to induce—or select for—resistance to the macrolide-lincosamide-streptogramin (MLS$_B$) group of antibiotics among respiratory and nonrespiratory pathogens.

This study explored the efficacy of telithromycin compared with the macrolide azithromycin in eradicating S pneumoniae from the nasopharynx of patients with acute maxillary sinusitis (AMS).

### METHODS

The patients were seen consecutively in an otolaryngology clinic and were diagnosed as having acute bacterial maxillary sinusitis. None had had ear or sinus infection for at least 1 month before their initial visit, and they had not received antimicrobial therapy for at least 6 weeks. Antimicrobial dosages were those recommended by the manufacturer and were chosen by the treating physicians according to the patients’ needs. A total of 105 patients (59 treated with telithromycin and 46 with azithromycin) were evaluated. Patients’ ages ranged from 18 to 64 years (mean age, 43 years), and 38 were males. Included in the final analysis were only those whose first culture showed bacterial growth of a potential pathogen. Patients were treated with either 500 mg/d of azithromycin for 3 days or 800 mg/d of telithromycin for 5 days. Compliance with administration of antimicrobials was evaluated in all instances by examining the unused amount of medication. No correlation with clinical efficacy was made. The study was granted institutional review board approval.

Patients’ symptoms lasting between 10 to 30 days and their complaints included facial pain, frontal headache, purulent nasal discharge, fever, or malaise. Occipitomental, lateral, oblique, and ventricomental views or computed tomography were obtained. Sinusitis was defined radiographically as complete sinus opacity, an air-fluid level or mucous membrane thickening of at least 6 mm in the maxillary sinus. For the occipitomental view, mucosal thickening of the maxillary sinuses was measured as the shortest distance from the air-mucosal interface to the most lateral part of the maxillary sinus wall.

Nasopharyngeal cultures were obtained before therapy and on a follow-up visit 10 to 12 days after initiation of antimicrobial therapy. These were obtained with calcium alginate swabs that were immediately plated into media supportive of the growth of aerobic bacteria. Specimens were processed semiquantitatively, and organisms were identified using conventional methods. Five colonies of each pathogen were picked up for analysis. All isolates of S pneumoniae were screened for penicillin susceptibility with a 1-µg oxacillin disk by the Kirby-Bauer disk diffusion method. Intermediate resistance to penicillin was defined as a minimal inhibitory concentration (MIC) of 0.1 to 1.0 µg/mL, and high resistance to penicillin was defined as an MIC greater than or equal to 2.0 µg/mL.

Minimal inhibitory concentrations were determined using the National Committee for Clinical Laboratory Standards broth microdilution method with Mueller-Hinton broth, supplemented with 5% lysed horse blood.$^{12,13}$ A final inoculum of 7 × 10$^4$ to 1 × 10$^5$ was used; microtiter plates were incubated at 36.5°C/ambient air for 16 to 20 hours. Minimal inhibitory concentration end points were read as the lowest concentration of antimicrobial that totally inhibited macroscopically visible growth of the inoculum. Standard quality control strains (ATCC) were included in each run. Isolates were tested against penicillin G, azithromycin, and telithromycin. Susceptibilities were calculated based on NCCLS breakpoints, also using the NCCLS tentative breakpoints for telithromycin. In addition, MICs of azithromycin were read after an additional 24 hours of incubation.

$\beta$-Lactamase production was determined by the chromogenic cephalosporin methods by using nitrocefin as the substrate.$^{14}$ Statistical analysis was performed using the t test and $\chi^2$ analysis with continuity correction.

### RESULTS

Of the 105 patients (59 treated with telithromycin and 46 with azithromycin) included in the study, pathogenic bacteria were recovered in 57 (32 treated with telithromycin and 25 treated with azithromycin). Sixty-seven potential pathogens were recovered prior to therapy in 57 patients, 32 treated with telithromycin and 25 treated with azithromycin: 5 pneumoniae (31 isolates), Haemophilus influenzae (non–type b) (13), Staphylococcus aureus (8), S pyogenes (8), and Moraxella catarrhalis (7) (Table). The distribution of the pathogens was similar in both groups. All M catarrhalis, 6 H influenzae, and 7 S aureus produced $\beta$-lactamase. The growth of all isolates was moderate to heavy. A single pathogen was recovered in 46 patients, 2 were found in 6, and 3 in 3. Following therapy the number of pathogens was reduced to 31 (Table).

Of the 14 S pneumoniae isolates recovered prior to therapy from the azithromycin group, 7 were resistant to penicillin (4 intermediately resistant and 3 highly re-

<table>
<thead>
<tr>
<th>Organism</th>
<th>Azithromycin, 500 mg/d</th>
<th>Telithromycin, 800 mg/d</th>
<th>Total</th>
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<tr>
<td>Staphylococcus aureus, No.</td>
<td>Pretherapy</td>
<td>Posttherapy*</td>
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</tr>
<tr>
<td></td>
<td>3</td>
<td>5</td>
<td>8</td>
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<tr>
<td>Moraxella catarrhalis, No.</td>
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<td>Posttherapy*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Streptococcus pyogenes, No.</td>
<td>Pretherapy</td>
<td>Posttherapy*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>2/0</td>
<td>5</td>
</tr>
<tr>
<td>Haemophilus influenzae, No.</td>
<td>Pretherapy</td>
<td>Posttherapy*</td>
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</tr>
<tr>
<td></td>
<td>6</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Streptococcus pneumoniae, No.</td>
<td>Pretherapy</td>
<td>Posttherapy*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>17</td>
<td>31</td>
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<tr>
<td>Total</td>
<td>Pretherapy</td>
<td>Posttherapy*</td>
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</tr>
<tr>
<td></td>
<td>29</td>
<td>38</td>
<td>67</td>
</tr>
</tbody>
</table>

*Data are given as number of isolates/number of isolates where minimal inhibitory concentration increased by at least 2 tubes. Cultures were obtained 10 to 12 days after initiation of therapy.
†P<.01 compared with other group.
‡P<.05 compared with other group.
sistant), 4 were resistant to macrolides, and none were resistant to telithromycin. Of the 17 S pneumoniae isolates in the telithromycin group prior to therapy, 9 were resistant to penicillin (6 intermediate resistant and 3 highly resistant), 6 were resistant to macrolides, and none were resistant to telithromycin.

The number of S pneumoniae isolates in the azithromycin group was reduced following treatment from 14 to 8 (43% reduction), 3 intermediate resistant and 2 highly resistant to penicillin, and 5 were resistant to macrolides. All but 1 isolate were recovered from the same individual. In contrast, the number of S pneumoniae isolates in the telithromycin group was reduced following treatment from 17 to 1 (94% reduction). This isolate was immediately resistant to penicillin and susceptible to azithromycin and telithromycin (P < .01) (Table).

No differences were noted in the eradication rate of all other groups of isolates that were all susceptible to both azithromycin and telithromycin.

Development of resistance to the antimicrobial agents used (defined as increase in the MIC by at least 2 tubes) was found only in 5 isolates (4 S pneumoniae and 1 H influenzae) recovered only from patients who received azithromycin (P < .05) (Table).

**COMMENT**

These data illustrate a better efficacy of telithromycin compared with azithromycin in the eradication of S pneumoniae from the nasopharynx of patients with AMS. In contrast, both therapies were equally active in the eradication of H influenzae, M catarrhalis, S pyogenes, and S aureus.

The upper respiratory tract, including the nasopharynx, serves as the reservoir for pathogenic bacteria that can cause respiratory infections such as sinusitis. Jousimies-Somer et al15 found good correlation between the composition of the nasopharynx and the organisms recovered from the acutely infected sinus. When the sinus aspirate culture yielded a presumed sinus pathogen, the same organism was found in the nasopharynx sample in 91% of the 185 evaluated patients. The predictive value of a pathogen-positive nasopharynx finding was high for S pyogenes (94%), H influenzae (78%), and S pneumoniae (69%) but was low for M catarrhalis (20%).

Telithromycin is a semisynthetic antibacterial agent belonging to a class of drugs called ketolides, which are a variation on the existing class of macrolides, whose structure includes a 14-molecule ring. The Food and Drug Administration approved telithromycin for use as a treatment for acute exacerbation of chronic bronchitis, community-acquired pneumonia, and acute bacterial sinusitis. Telithromycin fulfills a role that has arisen owing to the rise of microbial resistance to existing macrolides and seems to be effective against macrolide-resistant S pneumoniae. The defining differentiating characteristic of the ketolides as opposed to other macrolides is the removal of the neutral sugar, L-cladinose, from the 3 position of the macrocyclic ring and the subsequent oxidation of the 3-hydroxyl to a 3-keto functional group.16

These findings are supported by the study by Dohar et al17 who examined the prevalence of antibacterial resistance in 1336 bacterial pathogens, isolated from adult and pediatric patients clinically diagnosed with acute bacterial sinusitis. In total, 58.0%, 66.1%, and 55.8% of isolates were susceptible to penicillin, cefuroxime, and clarithromycin, respectively. Combined macrolide resistance and reduced susceptibility to penicillin was present in 200 (31.3%) of 640 S pneumoniae isolates, whereas 99.5% and 95.5% of isolates were susceptible to telithromycin and amoxicillin-clavulinate, respectively.

Our findings support the clinical data generated by Roos et al,18 Buchanan et al,19 and Luterman et al20 who documented the clinical efficacy of telithromycin in the treatment of AMS. Roos et al18 studied the efficacy of telithromycin given either for 5 or 10 days in 341 patients with AMS. A clinical cure rate of 91% was observed in each of the therapy groups. Buchanan et al19 compared 5 days of telithromycin with 10 days of cefuroxime-axetil therapy in 593 patients with AMS. Clinical cure was achieved in 85.2% of patients treated with telithromycin and 82.0% of patients treated with cefuroxime-axetil. Luterman et al20 compared the clinical efficacy of telithromycin, given for 5 or 10 days, with that of amoxicillin–clavulanic acid, given for 10 days, in 754 adults with AMS. Therapeutic equivalence of about 75% was demonstrated among the 3 therapy groups.

This study also illustrates the higher recovery rate of antimicrobial resistant pathogens from the nasopharynx of patients following azithromycin therapy compared with telithromycin. These findings are supportive of previous reports21,22 that illustrated the development of antimicrobial resistance following azithromycin therapy. Azithromycin therapy seems to put selective pressure on the infective and native flora of children, promoting the carriage of macrolide-resistant strains. The long elimination half-life of azithromycin allows subinhibitory serum and epithelial lining fluid concentrations over a period of several weeks posttreatment, which may have an impact on the emergence of macrolide resistance.

Further studies of the microbiology and effect of telithromycin therapy in AMS and other respiratory tract infections are warranted. These studies should investigate whether the use of telithromycin will be able to enhance recovery and reduce the occurrence of recurrences in these infections.

In conclusion, these data illustrate the superiority of telithromycin to azithromycin in the eradication of S pneumoniae from the nasopharynx. Both therapies were equally active in the eradication of H influenzae, M catarrhalis, S pyogenes, and S aureus.

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REFERENCES