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Comparison of Dirithromycin and Penicillin for Treatment of Streptococcal Pharyngitis

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In the treatment of group A β-hemolytic streptococcal pharyngitis, penicillin is the drug of choice and erythromycin is the alternative. In a double-blind, randomized study, dirithromycin, a new macrolide, was compared with penicillin for the treatment of streptococcal pharyngitis. Of 121 patients who were treated with dirithromycin, 96.7% manifested a favorable clinical response, and of 136 patients treated with penicillin, 94.2% manifested a favorable clinical response. Streptococci were eradicated from the pharynges of 85.3% of 116 dirithromycin-treated patients and 82.5% of 126 penicillin-treated patients who returned for follow-up. There were no statistically significant differences in efficacy between the two groups. The incidence of abdominal symptoms was higher in dirithromycin-treated patients. Being as efficacious as penicillin and having the advantages over erythromycin of once-daily dosing and the lack of drug interactions, dirithromycin is an alternative to penicillin in the treatment of streptococcal pharyngitis for patients 12 years of age and older.

Penicillin is the drug of choice for the treatment of group A streptococcal pharyngitis (5). For those unable to take penicillin, erythromycin is the recommended alternative (5). Although erythromycin is safe and effective, it has disadvantages. It is given two to four times daily, a regimen that precludes optimal compliance by patients compared with a regimen of once-daily dosage (7). Because it is metabolized by the cytochrome P-450 enzymes, erythromycin is involved in drug-drug interactions with other drugs that are metabolized by the same enzymes (15). Some of these interactions can be serious. Dirithromycin is a new macrolide antibiotic with in vitro activity against *Streptococcus pyogenes* (10). After oral administration, dirithromycin's ability to penetrate tissue results in sustained intratonsillar concentrations that exceed its MICs for *S. pyogenes*, suggesting its usefulness in the treatment of streptococcal pharyngitis (4). In clinical trials, dirithromycin was as effective and as safe as erythromycin in the treatment of streptococcal pharyngitis (6, 12). Because of its long half-life, dirithromycin can be given once a day (16). Unlike erythromycin, dirithromycin does not bind to cytochrome P-450 (11). In pharmacokinetic studies, dirithromycin did not manifest clinically significant interactions with theophylline, cyclosporine, and terfenadine (1–3, 8). Here, we show that dirithromycin is as efficacious as oral penicillin in the treatment of streptococcal pharyngitis.

MATERIALS AND METHODS

This was a multicenter, double-blind, double-dummy, randomized, parallel study in which 15 North American investigators participated.

Patients. Patients were matched for age, sex, height, weight, and ethnic origin. Approval was obtained from each investigative center's ethics committee. Eligible patients met the following criteria: (i) age of 12 years or older and weight of at least 81 lb, (ii) a diagnosis of streptococcal pharyngitis as described below, (iii) an informed consent approved by the institutional review board and signed by the patient or the patient's parent or guardian, (iv) an ability to return for follow-up examinations, and (v) for women of childbearing potential, a negative pregnancy test and the use of a reliable method of contraception during therapy and for 30 days thereafter.

A patient was excluded from the study for the following reasons: (i) any condition precluding evaluation of response to treatment, (ii) known or anticipated requirement of systemic antibiotics other than the study antibiotic, (iii) hypersensitivity to macrolides, penicillins, or cephalosporins, (iv) pregnancy or breast-feeding, (v) use of any systemic antibiotics in the 7 days before the study, and (vi) participation in a previous dirithromycin study or any study involving an investigational drug in the 30 days prior to this study.

Antibiotics and dosages. Dirithromycin was given at a dosage of 500 mg (two 250-mg tablets) once daily for 10 days. Penicillin VK was given at a dosage of 250 mg four times daily for 10 days. Differences in compliance were avoided by the double-dummy design. This was accomplished by giving two bottles to each patient, one containing 20 tablets (dirithromycin or placebo) and one containing 40 capsules (penicillin or placebo). Patients in the dirithromycin group received two 250-mg tablets of dirithromycin once daily and one placebo capsule four times daily and the patients in the penicillin group received two placebo tablets once daily and one penicillin capsule four times daily. In addition, compliance was monitored by having the patients return the bottles at the posttherapy visit and having the investigators record the number of remaining tablets or capsules. As measured by this pill-counting technique, there were no differences in compliance between the two groups of patients.

The patients were given numbers. The study drug kits supplied to investigators contained the medicines and diagnostic materials. To ensure a balanced randomization and blinding, investigators could identify the study kits only by numbers which had been generated by a computer program. Patients and investigators were both blinded. The randomization list was not provided to the investigators until the study was complete and the database had been declared accurate and complete.

Procedures. A complete history was taken and a physical examination was performed. Streptococcal etiology was presumed on the basis of a rapid streptococcal antigen test (Hybritech ICON Strep A assay) while awaiting subsequent confirmation by culture. Patients with negative cultures for group A streptococci were excluded from the study. Throat swabs obtained by swabbing both tonsils or tonsillar fossae and the posterior oropharynx (avoiding the tongue and buccal mucosa) with a sterile rayon swab were cultured onto 5% sheep blood–Trypticase soy agar by previously published methods (9). The isolated group A streptococci were tested for their sensitivities to the study drugs by methods recommended by the National Committee for Clinical Laboratory Standards (13, 14). Organisms were considered sensitive to dirithromycin when the MIC for the organism was ≤2 μg/ml and were considered sensitive to penicillin when the MIC was ≤0.12 μg/ml. Cultures were obtained before therapy, during therapy, and at the posttherapy and late posttherapy visits. All isolated streptococci were tested for susceptibility. Clinical symptoms and signs were assessed and pharyngeal swabs obtained during days 3 to 5 of therapy, 3 to 5 days after completing therapy, and 3 to 5 weeks after completing therapy were cultured. When an adverse event occurred, a clinical examination and appropriate laboratory tests were done. Patients or their parents or guardians were instructed to call the investigator if an adverse event occurred.

Clinical responses were defined as follows: cure, elimination of signs and

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TABLE 1. Demographic profile of patients

Demographic feature[a]	Treatment group	
	Dirithromycin (n = 170)[b]	Penicillin (n = 175)
Sex (no. of males/no. of females)	62/108	63/112
Mean age (yr)	28.3 ± 9.7	29.0 ± 9.4
Mean ht (cm)	168.1 ± 12.0	168.6 ± 10.0
Mean wt (kg)	71.9 ± 18.0	72.3 ± 18.0
Ethnic origin (%)		
Caucasian	82.9	83.4
Black	7.6	4.6
Hispanic	7.6	9.1
Asian	1.8	1.1
Other	0.0	1.7

[a] None of the differences was statistically significant.
[b] n, total number of patients enrolled.

symptoms; improvement, significant but incomplete resolution of signs and symptoms; relapse, worsening of signs and symptoms after initial improvement; and failure, no improvement in signs and symptoms during treatment.

Bacteriological responses were defined as follows: eradication, the organism was eradicated; persistence, the culture was positive for the original pathogen (same serotype); relapse, after initial eradication at the during-therapy visit or posttherapy visit, recurrence of the same pathogen (same serotype) with or without the development of resistance; eradication with reinfection, the culture was positive for a new pathogen (new serotype) after the conclusion of therapy (patients had to fail symptomatically or have a relapse); colonization, the culture was positive for a new serotype without the signs of infection; presumed microbial persistence, the culture was negative but a new antibiotic for the treatment of streptococcal pharyngitis was started; indeterminate, unable to evaluate a new antibiotic was started for a condition other than the study indication). For serotyping, paired isolates from patients having positive follow-up cultures were sent to a reference laboratory (E. Kaplan, World Health Organization Collaborating Center for Reference and Research on Streptococci, University of Minnesota, Minneapolis).

A patient was discontinued from the study for the following reasons: (i) completion of the protocol, (ii) symptomatic or bacteriologic failure, (iii) recovery of a resistant pathogen, (iv) a side effect that necessitated discontinuation, (v) withdrawal by the patient, parent, guardian, or investigator, (vi) unblinding for safety or other reasons, (vii) a negative pretreatment culture, (viii) requirement for treatment with another antibiotic, (ix) exclusion criteria found after enrollment, and (x) safety reasons.

Statistical methods. Statistical differences between study groups for categorized variables were assessed by chi-square tests. For the statistical analysis of continuous data, the two-sample t test on ranked data was used.

RESULTS

The patients who received either dirithromycin or penicillin were similar demographically with respect to age, sex, height, weight, and ethnic origin (Table 1). Of 170 patients enrolled in the dirithromycin group, 121 patients were qualified for efficacy analysis. Of 175 patients enrolled in the penicillin group, 136 patients were qualified for analysis (Table 2). The evaluable patients in each group were also similar demographically. One or more concomitant drugs were used during therapy by 52.9% of the dirithromycin-treated patients and by 57.1% of the penicillin-treated patients. Of the medicines taken concomitantly, acetaminophen was used most frequently. It was used by 27.1% of dirithromycin-treated patients and 26.3% of penicillin-treated patients. There were no significant differences between the two groups in the presenting clinical conditions: in the dirithromycin group, 75.9% of patients had pharyngitis and 24.1% had tonsillitis; in the penicillin group, 72.6% had pharyngitis and 27.4% had tonsillitis. Investigators assessed 6.5% of the patients treated with dirithromycin and 4.0% of patients treated with penicillin as "seriously" ill. In summary, the randomization procedure resulted in two treatment groups matched well with respect to demographics, baseline diagnosis, concomitant treatments, and clinical condition.

TABLE 2. Reasons for discontinuing patients from study

Reason for discontinuation[a]	No. (%) of patients	
	Dirithromycin (n = 170)[b]	Penicillin (n = 175)
Study completed	104 (61.2)	109 (62.3)
Lack of efficacy	20 (11.8)	26 (14.9)
Lost to follow-up	4 (2.4)	1 (0.6)
Patient's decision	3 (1.8)	0
Entry criteria exclusion	25 (14.7)	22 (12.6)
Protocol violation	8 (4.7)	8 (4.6)
Adverse event	6 (3.5)	9 (5.1)

[a] In the dirithromycin group, 121 patients qualified for efficacy analysis, including 18 patients who were terminated from the study because of a lack of efficacy (of the 20 patients for whom there was a lack of efficacy, 2 were disqualified because the bacteriological diagnosis was not confirmed) and 103 patients who completed the protocol (1 of the 104 patients who completed the study was excluded from evaluation because of violation of an entry criterion). In the penicillin group, of the 136 patients who qualified, 109 completed the protocol, 26 patients were discontinued because of a lack of efficacy, and 1 patient discontinued because of an adverse event.
[b] n, number of patients enrolled.

During therapy (at 3 to 5 days), cultures became negative for 114 of 121 (94.2%) patients given dirithromycin and 133 of 136 (97.8%) patients given penicillin. Among the patients given dirithromycin, six of seven patients who had positive cultures during therapy failed to eradicate the organisms at subsequent posttherapy visits and thus were bacteriological failures, and among the patients treated with penicillin, two of three patients with positive cultures during therapy were bacteriological failures.

Of the 121 patients who took dirithromycin, 96.7% had a favorable clinical response 3 to 5 days after treatment, whereas 94.2% of the 136 patients who took penicillin had a favorable clinical response (Table 3). In the 3 to 5 days after treatment, streptococci were eradicated from 90.1% of the patients taking dirithromycin and 90.4% of the patients taking penicillin (Table 3). These differences in clinical and bacteriological responses were not statistically significant.

Among the patients who returned for examination 3 to 5 weeks after treatment, streptococci were eradicated from the

TABLE 3. Clinical and bacteriological responses 3 to 5 days after treatment

Response	No. (%) of patients	
	Dirithromycin (n = 121)[a]	Penicillin (n = 136)
Clinical response[b]		
Cure	95 (78.5)	101 (74.3)
Improvement	22 (18.2)	27 (19.9)
Relapse or failure	4 (3.4)	8 (5.8)
Bacteriological response[c]		
Eradication	109 (90.1)	123 (90.4)
Colonization	1 (0.8)	1 (0.7)
Persistence	3 (2.5)	1 (0.7)
Relapse	7 (5.8)	11 (8.1)
PMP[d]	1 (0.8)	0

[a] n, number of qualified patients.
[b] None of the differences in responses was statistically significant.
[c] The definition of each bacteriological response is given in the text.
[d] PMP, presumed microbial persistence (defined in the text).

TABLE 4. Bacteriological responses 3 to 5 weeks after treatment

Response[a]	No. (%) of patients	
	Dirithromycin (n = 116)[b]	Penicillin (n = 126)
Eradication	99 (85.3)	104 (82.5)
Relapse	11 (9.5)	18 (14.3)
Eradication then reinfection	1 (0.9)	2 (1.6)
PMP[c]	4 (3.4)	1 (0.8)
Indeterminate	1 (0.9)	2 (0.8)

[a] None of the differences in responses between the two groups was statistically significant.
[b] n, number of qualified patients who returned for evaluation.
[c] PMP, presumed microbial persistence (defined in text).

TABLE 5. Incidence of adverse events

Adverse event	No. (%) with events	
	Dirithromycin (n = 170)[a]	Penicillin (n = 175)
Headache	29 (17.1)	38 (21.7)
Dizziness	2 (1.2)	6 (3.4)
Asthenia	4 (2.4)	7 (4.0)
Nausea[b]	26 (15.3)	10 (5.7)
Vomiting	2 (1.2)	8 (4.6)
Diarrhea	25 (14.7)	15 (8.6)
Abdominal pain[b]	23 (13.5)	11 (6.3)
Dyspepsia	14 (8.2)	8 (4.6)
Discontinuation of drug[c]	6 (3.5)	9 (5.1)

[a] n, number of patients enrolled who received the drug.
[b] Statistically significant (P <0.05).
[c] Reasons for discontinuations are given in text.

pharynges of 85.3% of the 116 patients who took dirithromycin and 82.5% of the 126 patients who took penicillin (Table 4). These differences were not statistically significant.

Of the 345 patients enrolled in the study, 7 were excluded from the study because the organisms isolated were resistant to dirithromycin. None were found to be resistant to penicillin. Of the seven patients infected with organisms resistant to dirithromycin, two were in the penicillin group and five were in the dirithromycin group. Of the five in the dirithromycin group, four received full courses of treatment with dirithromycin, two of these patients were cured of their symptoms and bacteria were eradicated from both of them. The three remaining patients were bacteriological failures, although a favorable clinical response was seen in all three patients. The MICs for the organisms isolated pretherapy from the 121 evaluable dirithromycin-treated patients varied from 0.06 to 0.5 μg/ml for dirithromycin. Among these patients who failed to eradicate the organisms, only one isolate became resistant after therapy (pretherapy MIC, 0.063 μg/ml; posttherapy MIC, 8.0 μg/ml). Among the organisms for the 136 patients who were treated with penicillin, the MICs for the isolated organisms were 0.060 or 0.12 μg/ml. Of the group A streptococci isolated at the posttherapy visit from the penicillin-treated patients with bacteriological failures, none had become resistant to penicillin.

Whether it was caused by the test drug or not, any untoward event reported by the patient during the study was defined as an adverse event. Adverse events are given for all patients who took study drugs, including patients whose data were excluded from the analysis of data for efficacy. Adverse events were reported by 108 (63.5%) of the 170 patients who took dirithromycin and 118 (67.4%) of the 175 patients who took penicillin (Table 5). Six patients receiving dirithromycin discontinued the drug because of an adverse event: hives, abdominal pain, dyspepsia, anxiety, menstrual cramps, and appendectomy. Nine penicillin-treated patients discontinued the drug because of dizziness, diarrhea, abdominal pain, rash (two patients), vomiting, urinary tract infection, vaginal bacterial infection, and nausea. Of the various side effects encountered, the higher incidences of nausea and abdominal pain in patients given dirithromycin were statistically significant. There were no deaths. Neither drug caused a serious adverse event.

DISCUSSION

In this study, dirithromycin and penicillin were equally efficacious in the treatment of group A streptococcal pharyngitis. Rates of favorable clinical response and bacteriological eradication were equivalent. The incidence of abdominal pain and nausea was higher in patients taking dirithromycin than in those taking penicillin. However, only 3 of 170 patients stopped taking dirithromycin because of abdominal symptoms. In earlier studies, dirithromycin was as effective and as safe as erythromycin in treating streptococcal pharyngitis (6, 12). With the advantages over erythromycin of once-daily dosing, a high level of penetration into tissue, and a lack of drug-drug interactions, dirithromycin is an alternative to penicillin in the treatment of streptococcal pharyngitis in patients 12 years of age and older.

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