Clarithromycin vs Penicillin in the Treatment of Streptococcal Pharyngitis

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Background. Streptococcal pharyngitis, caused by group A β-hemolytic streptococci (GABHS), is among the most common infections seen by primary care physicians. Because the illness can result in rheumatic fever, early eradication of infection is important. Penicillin has been the standard treatment for GABHS pharyngitis for over four decades, but reports of bacteriologic failure with this drug in recent years have led to trials of alternative antimicrobials.
Methods. In this investigator-blind, randomized multicenter trial (30 centers), oral clarithromycin, 250 mg twice daily, or oral penicillin VK, 250 mg three times daily, was given to outpatients ≥12 years old with GABHS pharyngitis as documented by positive cultures for *Streptococcus pyogenes* and positive rapid immunoassay tests. The clinical and bacteriologic efficacy of clarithromycin was compared with that of penicillin in the 356 evaluable patients. Safety analysis was performed in all patients who had received at least one dose of the study drug (N = 453).
Results. Overall, clinical outcomes were comparable in the two groups. However, more clarithromycin-treated patients than penicillin-treated patients had resolution of sore throat (94% vs 86%, $P = .014$) and disappearance of pharyngeal erythema and exudate (89% vs 82%, $P = .05$). Bacteriologic cure rates were higher in clarithromycin-treated patients (95% vs 87%, $P = .009$). No serious adverse events were observed in either group.
Conclusions. This study suggests that clarithromycin twice daily is as effective and as well tolerated as penicillin in the treatment of streptococcal pharyngitis.
Key words. Clarithromycin; penicillin; streptococcal infections; pharyngitis; rheumatic fever.
J Fam Pract 1992; 35:622-626.

Streptococcal pharyngitis is caused by *Streptococcus pyogenes*, a group A β-hemolytic streptococcus (GABHS), and is among the most common conditions treated by primary care physicians in the United States.[1] An estimated $300 million is spent on the diagnosis and treatment of this illness each year.[2] Effective treatment is important to prevent the suppurative complications and reduce the incidence of subsequent rheumatic fever.

Penicillin, introduced in the 1940s, has been the standard treatment for patients with GABHS pharyngitis and other streptococcal illness. Early studies demonstrated 93% to 99% eradication of GABHS from the pharynx following penicillin treatment.[3,4] Recent studies, however, have found a pharyngeal persistence of GABHS in 11% to 21% of patients following intramuscular or oral administration of penicillin.[5–9] This finding and the high incidence of penicillin allergy have stimulated the development and evaluation of alternative antimicrobial drugs for the treatment of GABHS pharyngitis.

Clarithromycin, a new generation macrolide antibiotic, has a structure similar to that of erythromycin except for substitution of the hydroxyl group at position six of the macrolide ring by an O-methyl(CH_3O) group. Clarithromycin is twice as active as erythromycin and is as active against GABHS in vitro as penicillin. Clarithromycin has an improved pharmacokinetic profile with more consistent serum levels, allowing twice-daily administration. Oral absorption is unaffected by food intake, and administration need not be timed with respect to meals. The drug has been found to diffuse well into tonsillar tissue.[10]

The purpose of this randomized, investigator-blind multicenter study was to compare the efficacy of orally administered clarithromycin with that of penicillin VK (potassium salt of phenoxymethyl penicillin) in the treatment of patients diagnosed clinically and bacteriologically as having pharyngitis caused by GABHS. Comparative safety analyses were also performed.

Submitted, revised, April 30, 1992.

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 ISSN 0094-3509

Methods

Patients

Initially, 453 outpatients (270 male, 183 female) at least 12 years of age were enrolled in the study. All had sore throat caused by group A β-hemolytic streptococci, as confirmed by a positive rapid immunoassay test for group A streptococcal antigen and a positive culture for *Streptococcus pyogenes* or immunoassay results positive for this organism. To qualify for immunoassay and culture, patients had to have at least one sign or symptom of streptococcal pharyngitis: pharyngeal erythema or exudate, tenderness of cervical lymph nodes, or fever. Also, the streptococcal pharyngitis had to be an initial episode and not a recurrence.

Patients were excluded from the study if they had a history of hypersensitivity to erythromycin or penicillin, rheumatic fever, cardiac valvular disease, allergies, or asthma, or if they were women at risk of pregnancy. Patients were also excluded if they had any clinically significant hematologic abnormalities, hepatic or renal disease, or a rash suggestive of scarlet fever. They could not have received treatment with a systemic antibiotic within 2 weeks before the study, a penicillin injection within 6 weeks, or an experimental drug within 4 weeks. Patients were not accepted if they were concurrently receiving an antimicrobial drug, theophylline, digitalis, glycosides, warfarin, ergotamine, or carbamazepine.

All of the 453 patients enrolled in the study were eligible for safety analysis by virtue of having taken at least one dose of the study drug. Of these, 356 patients met the criteria for efficacy analysis (described below).

Study Design

The study was a single-blind (investigator-blind) randomized clinical trial of clarithromycin and penicillin VK in outpatients with a confirmed diagnosis of group A β-hemolytic streptococcal pharyngitis. Investigators at 30 clinics throughout the United States—mostly private family practice offices—enrolled patients in the study (see Acknowledgments). Patients were randomized in a 1:1 ratio at each center to receive either clarithromycin, 250 mg every 12 hours, or penicillin VK, 250 mg every 8 hours; both study drugs were supplied as 125-mg capsules. Recommended duration of treatment was 10 days. Compliance was monitored by pill counts at each visit.

Efficacy was assessed by both clinical and bacterial response variables. Patients were considered evaluable for efficacy analyses if they received at least 7 days' treatment with the study drug and underwent clinical and bacteriologic evaluation within 4 to 6 days after completion of treatment. Patients who were discontinued because of clinical or bacteriologic failure were considered eligible for efficacy analysis, whereas those discontinued for other reasons were not eligible.

The study was approved by the institutional review boards of all participating medical centers, and all patients gave written informed consent after the purpose of the study and procedures were explained in full.

Clinical Evaluation

Before treatment was started, patients underwent a complete physical examination including assessment of clinical signs and symptoms; an eye examination; and laboratory tests, including hematology and coagulation tests, serum chemistry, and urinalysis (visit 1). Sore throat was graded as *absent, mild, moderate*, or *severe*. The presence or absence of the following were noted: abdominal pain within 24 hours before therapy, pharyngeal erythema or exudate, cervical lymph node tenderness, and fever, absent (<100°F [<37.8°C]) or present (≥100°F [≥37.8°C]).

After 5 to 7 days of treatment (visit 2), patients returned for a repeat assessment of clinical status as outlined above. Within 4 to 6 days after termination of antibiotic treatment (visit 3), patients again returned for post-treatment clinical evaluation. Finally, follow-up evaluation was performed 19 to 25 days post-treatment (visit 4).

Clinical response was determined by comparing pretreatment clinical signs and symptoms with those observed post-treatment at either visit 3 or visit 4. Patients were classified as *clinically cured* if their pretreatment signs and symptoms of infection resolved and *clinically improved* if their signs and symptoms lessened but did not resolve. They were considered a *clinical failure* if their condition was unchanged or worsened. When a clinical response could not be assigned, the patient's status was categorized as *indeterminate*.

Bacteriologic Evaluation

At the pretreatment evaluation (visit 1) a throat culture was obtained and a rapid immunoassay for group A streptococcal antigen was performed. Throat cultures were obtained by swabbing the posterior pharynx and both tonsils or tonsillar fossae with two Dacron swabs held together. One swab was tested for the presence of *S pyogenes* using Abbott TestPack Strep A. The second swab was cultured to confirm the diagnosis of streptococcal pharyngitis. All cultures positive for *S pyogenes* were subcultured and stored at −70°C for group A serotyping. In vitro susceptibilities were determined by

disc diffusion technique (Protocol M2A4, National Committee for Control of Laboratory Standards, 1990). Results were recorded as *susceptible*, *intermediately susceptible*, or *resistant*. Only patients whose pretreatment throat cultures were positive for *S pyogenes* and were rated susceptible or intermediately susceptible were included in efficacy analyses.

After 5 to 7 days of antibiotic treatment, patients underwent throat culture (visit 2). This was repeated 4 to 6 days after the end of treatment (visit 3), and at follow-up 19 to 25 days post-treatment (visit 4).

Bacteriologic response was categorized as *eradicated* if the initial pathogen, *S pyogenes*, was not isolated from throat cultures at visit 3 and as *persistent* if the organism was isolated at that visit. Bacteriologic response was considered *recurrent* if the pretreatment pathogen was eradicated by visit 3 but reappeared at visit 4. If the patient's pretreatment pathogen was eradicated at visit 3 but a new strain of *S pyogenes* appeared at visit 4, reinfection was assessed. A bacteriologic response that could not be assessed was categorized as *indeterminate*.

Safety Assessment

All patients who received at least one dose of the study drug were evaluable for safety assessment. Adverse events were rated as *mild*, *moderate*, or *severe* depending on whether they were transient and easily tolerated by the patient, caused discomfort, or incapacitated the patient, respectively. The relationship of the adverse event to administration of the study drug was assessed as either *probably related* or *possibly related*, depending on the presence or absence of a temporal relationship to drug treatment.

Statistical Analyses

Demographic variables, clinical responses, bacteriologic responses, and adverse reactions to clarithromycin and penicillin VK were analyzed by Fisher's exact test. Each comparison of treatment groups was two-sided with a .05 level of significance.

Results

Patients

Of the 453 patients enrolled in the study, 226 received clarithromycin and 227 received penicillin VK. The clarithromycin group consisted of 99 female and 127 male patients, ranging in age from 12 to 62 years (mean, 30 years) and weighing 78 to 317 lb (35 to 143 kg, mean 171 lb [77 kg]. In the penicillin group, there were 84 female and 143 male patients, ranging in age from 12 to 64 years (mean, 30 years) and weighing 80 to 336 lb (mean, 173 lb [78 kg]). Statistical analyses showed that the demographic variables of the two groups (sex, age, race, weight) did not differ significantly, nor did those of the subsets of patients evaluable for efficacy ($P \geq .05$). Baseline signs and symptoms in the two groups were comparable (Table 1). Duration of therapy for the majority of patients (85%) was 8 to 10 days.

Table 1. Percentage of Patients in the Clarithromycin and Penicillin VK Groups* Who Had Baseline Signs and Symptoms

Sign or Symptom	Clarithromycin	Penicillin VK
Sore throat (mild/moderate/severe)	10/40/50	9/42/49
Pharyngeal examination (normal/erythematous/exudate)	1/42/58	0/37/63
Abdominal pain	17	22
Tender lymph nodes	89	92
Headache	56	64
Fever	21	27

**No group differences were statistically significant.*

Of the 226 patients who received clarithromycin and the 227 who received penicillin, 179 and 177, respectively, were evaluable for efficacy analysis. The primary reason for exclusion in both groups was that *S pyogenes* was not identified in the pretreatment culture (23 and 30 patients, respectively). Other reasons for exclusion included the following: no pretreatment susceptibility data were available; no post-treatment cultures were available; patient received concomitant medication not allowed in the protocol; patient received less than 7 days of treatment with the study drug or was prematurely discontinued for a reason other than clinical or bacteriologic failure; or patient was lost to follow-up.

Streptococcus pyogenes pathogens were isolated from the pretreatment cultures of 400 patients. Of these, 382 (96%) were susceptible in vitro to both clarithromycin and penicillin VK.

Clinical Responses

At the post-treatment evaluation (visit 3), overall clinical success rates were comparable in the two treatment groups (Table 2). However, more clarithromycin-treated patients had resolution of sore throat than penicillin-treated patients (94% vs 86%, $P = .014$). Also, resolution of pharyngeal erythema or exudate was observed more frequently in clarithromycin-treated patients (89% vs 82%, $P = .05$). No significant differences were observed between treatment groups with respect to the following: resolution of lymph node tenderness (92%

Table 2. Rates of Clinical and Bacteriologic Response to Clarithromycin and Penicillin VK in Patients with Streptococcal Pharyngitis

Response	Post-treatment (Visit 3) Clarithromycin (n = 179)	Post-treatment (Visit 3) Penicillin VK (n = 177)	Follow-up (Visit 4) Clarithromycin (n = 110)*	Follow-up (Visit 4) Penicillin VK (n = 95)*
Clinical				
Cure	89	85	93	88
Improved	8	11	1	1
Failure	3	3	—	—
Relapse	—	—	6	10
Indeterminate†	0	1	3	10
Clinical success rate	97	97	94	90
Bacteriologic				
Cure	95‡	87	94	88
Failure	5	13	—	—
Reinfection	—	—	1	1
Recurrence	—	—	6	11
Indeterminate†	2	5	12	31
No data obtained	39	46	—	—

**The n values for visit 4 differ for those in visit 3 because the initial protocol did not require clinical evaluation at the time of follow-up (19 to 25 days after the initial visit). Bacteriologic evaluation, however, was required at follow-up, at which time 160 patients in the clarithromycin group and 135 in the penicillin VK group were evaluated.*

†Patients were included in the indeterminate category if confounding factors (eg, use of another antibiotic, a concurrent illness, culture specimen collected too late) rendered their data invalid.

‡The difference between the bacteriologic cure rates for patients treated with clarithromycin and those treated with penicillin was significant at P = .009.

and 90%, respectively), disappearance of abdominal pain (97% for both groups), and resolution headache (94% and 90%, respectively). All patients had resolution of fever except for one in the penicillin group.

Bacteriologic Responses

The bacteriologic cure rate post-treatment was significantly higher in the clarithromycin group than in the penicillin group (95% vs 87%, $P = .009$). Nine patients in the clarithromycin group had recurrence of their infection at follow-up, as compared with 15 in the penicillin group, but this difference was not statistically significant (Table 2).

Safety Analysis

When patient subgroups were analyzed for incidence of adverse events by investigator, sex, race, age, and duration of treatment, no significant differences were found. In the clarithromycin group, 8 patients (38%) reported at least one adverse event; this occurred in 82 penicillin-treated patients (36%). Nausea was the most common complaint among clarithromycin-treated patients (n = 10), while abdominal pain was the most common complaint among patients in the penicillin group (n = 9). No clinically significant changes in laboratory test results were found in either treatment group.

Discussion

Our results showed that clarithromycin was as effective as penicillin in the treatment of streptococcal pharyngitis. On two clinical outcome variables, results in clarithromycin-treated patients were better than those for penicillin-treated patients, ie, resolution of sore throat (94% vs 84%, $P = .014$) and disappearance of pharyngeal erythema or exudate (89% vs 82%, $P = .050$). Bacteriologic cure rates were also higher in clarithromycin-treated patients (95% vs 87%, $P = .009$).

The bacteriologic failure rate for penicillin observed in our study, 13%, is comparable to rates reported by others. In a meta-analysis of studies of penicillin treatment of GABHS pharyngitis between 1970 and 1989, Pichichero and Margolis[11] found that 16% of treated patients did not achieve bacteriologic cure. Three hypotheses have been advanced to explain what appears to be the declining efficacy of penicillin.[11] First, a larger number of resistant strains of GABHS may be emerging. Second, penicillin tolerance, defined as an isolate having higher minimum bactericidal concentration (MBC) than minimum inhibitory concentration (MIC) for penicillin, may be increasing. Third, β-lactamase–producing pharyngeal flora may inactivate penicillin.

In our study and studies performed by others,[12,13] no reduced susceptibility using standard testing has been demonstrated. We found that penicillin and clarithromycin were both active against 96% of the isolates tested.

Some authors have demonstrated penicillin tolerance in which GABHS is inhibited but not killed.[14] Kim and Kaplan[15] reported tolerance of 25% of GABHS isolates from patients classified as penicillin treatment failures. Penicillin-tolerant isolates may have played a role in our study as well, but specific testing was not carried out. In any event, clarithromycin is bactericidal against GABHS, and to date no tolerance has been reported with this agent.

Several authors have proposed that β-lactamase–producing copathogens in the pharynx of patients with GABHS pharyngitis are responsible for inactivating penicillin. In one report, a community outbreak of GABHS pharyngitis occurred in which patients failed to respond to penicillin treatment even though susceptibility testing indicated that the cultured streptococci were highly susceptible to the drug (MIC < .001 μg/mL). When 98 of these patients were subsequently treated with a 10-day course of clindamycin, a non–β-lactam drug, 96 were cured both clinically and bacteriologically.[16] One study

has demonstrated reduced bacteriologic recurrence rates with β-lactam–stable agents[17]; however, other studies have found no improvement in clinical or bacteriologic cure rates with β-lactam–stable agents.[18] In any case, clarithromycin, a non–β-lactam antibiotic, would not be inactivated by β-lactamases and therefore would not fail on this basis.

The patients in our study tolerated clarithromycin and penicillin well, with no significant differences in adverse event profiles. In another study comparing clarithromycin and erythromycin, patients treated with erythromycin had more severe adverse events than those treated with clarithromycin.[19]

Because clarithromycin is unrelated chemically to penicillin, it may be used in patients with a history of penicillin allergy. It is contraindicated in patients with allergy to erythromycin and, of course, to clarithromycin itself. The incidence and severity of allergic reactions to this compound are probably less than those observed with penicillin. In 19 clinical studies involving 2120 patients, only 1% of enrolled patients discontinued treatment with clarithromycin because of drug-related side effects.[13]

Compliance was required for inclusion in the evaluable-patient group in this study and therefore was not a factor in our results. However, compliance is a significant problem in clinical practice. The twice-daily dosing schedule for clarithromycin is an advantage over that of agents that must be administered more frequently, such as erythromycin. Also, administration of clarithromycin does not have to be coordinated with mealtimes.

In conclusion, we found clarithromycin to be as clinically effective as penicillin in the treatment of GABHS pharyngitis in the family practice setting, with slightly better bacteriologic effectiveness. Compliance may be enhanced by the twice-daily dosing regimen and by the low incidence of side effects.

Acknowledgments

This study was supported by a grant from Abbott Laboratories, Abbott Park, Illinois.

The following members of the Clarithromycin Study Group contributed patients to this clinical trial: Drs Pam K. Bamrah, Floyd Berk, Susan A. Diamond, M. Temple Douglas, Lynn D. Eggman, James C. Freudenburg, Kathleen Gallaher, James Geil, Curtis W. Hancock, Thomas Hunt, James J. Jerzak, Paul O. Kretschmar, Jeffrey H. Lamont, Howard M. Lebow, Dennis L. Lower, David A. Lucks, F. Benjamin Merritt, John F. Motley, Barry R. Paull, Gary L. Post, Joseph P. Repice, Norman J. Rosen, Robert N. Schulenberg, J. Timothy Sehy, John M. Stafford, Michael J. Unger, Julius H. Van Bavel, Gregory W. Weisshaar, James E. Willard.

Nancy Siepman, PhD, Abbott Laboratories Statistical Department, performed the statistical analyses.

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