Comparative In Vitro Activity of Moxifloxacin by E-test against *Streptococcus pyogenes*

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Macrolides are currently used to treat *Streptococcus pyogenes* infections where allergy or resistance prevents the use of penicillin. However, growing macrolide resistance is now seen worldwide, with rates of 5%–40% being reported. In this context it is therefore important to have other therapeutic options. The aim of this study was to ascertain the potential role of moxifloxacin, a third-generation fluoroquinolone, in the treatment of infections caused by group A *S. pyogenes*. The antimicrobial susceptibilities of *S. pyogenes* isolated from 197 adult patients with pharyngotonsillitis were analyzed by the E-test. Twelve percent of the isolates were resistant to macrolides, and 5% showed diminished susceptibility toward penicillin; none of the strains were resistant to cefotaxime or to moxifloxacin (90% minimum inhibitory concentration, 0.25 μg/mL). Therefore, moxifloxacin may be a therapeutic option in the management of *S. pyogenes* infections when penicillin cannot be used or when macrolide resistance may be a local issue. Clinical studies of moxifloxacin in pharyngotonsillitis are warranted.

*Streptococcus pyogenes* is the most common cause of bacterial pharyngitis, and penicillin G remains the drug of choice for the treatment of this condition. Strains susceptible to penicillin (MIC, ≤0.1 μg/mL) still account for up to 98% of isolates [1]. Furthermore, the clinical significance of penicillin-tolerant strains (minimum bactericidal concentration/MIC ratio, >32) remains uncertain [2]. However, for patients who are allergic to β-lactams or other antibiotics, macrolides generally must be used. In this context, of concern is the marked increase in the incidence of resistance to macrolides that has been seen over the last 20 years, particularly recently. The highest macrolide resistance rates have been reported in Italy; noteworthy was the rise from 5.1% in 1993 to 25.9% in 1995 [3]. In Spain, resistance rates to erythromycin rose from 1.2% in 1990 to 34.5% in 1995. One transient episode was reported in Finland in 1988, during which resistance rose to 42%. Rates subsequently declined after a reduction in macrolide usage [4, 5]. Analysis of available data from the United States indicates that macrolide resistance is <5% among *S. pyogenes* strains [6].

Third-generation fluoroquinolones have an extended spectrum that includes the gram-positive organisms—in particular, *Streptococcus pneumoniae*—that cause respiratory tract infections. Moxifloxacin, a new 8-methoxy quinolone, has good activity against *Streptococcus pneumoniae*—that cause respiratory tract infections. Moxifloxacin, a new 8-methoxy quinolone, has good activity against a range of gram-positive cocci and appears to select for resistant mutants much more slowly than older fluoroquinolones [7]. Also, the affected genes are apparently not the same, at least in *Staphylococcus aureus* [8].

With regard to resistance to fluoroquinolones, at least 1 *S. pyogenes* clinical isolate has been reported to be resistant to trovafloxacin, grepafloxacin, and others. The mechanism of resistance (single mutations in both the *parC* and *gyrA* genes) is similar to that reported for *S. pneumoniae* [9]. Because antibiotic usage in Mexico is far from rational—these drugs are sold over the counter—it is important to assess the local susceptibility of organisms to the recently developed fluoroquinolones as part of a worldwide assessment of sensitivities [10].

The objective of this study was to ascertain the potential role of moxifloxacin as a second treatment
choice to penicillin in upper respiratory tract infections caused by *S. pyogenes*. To this end, we tested the activity of moxifloxacin in vitro against *S. pyogenes* strains isolated from the upper respiratory tract.

**MATERIALS AND METHODS**

Adult patients in Mexico City with pharyngotonsillitis were sampled by throat swab. Samples were streaked onto blood-agar plates and incubated at 35°C for 24 h. Colonies showing the appropriate hemolysis pattern were isolated. Preliminary identification was performed with bacitracin disks, then by the API 20 Strep (bioMérieux) microbiochemistry kit. Strains were stored in brain-heart infusion broth containing 25% glycerol at −70°C.

Susceptibilities to the β-lactams, penicillin G and cefotaxime, the macrolides azithromycin and clarithromycin, and the third-generation fluoroquinolone moxifloxacin were assessed by the E-test method, following the manufacturer’s guidelines.

**RESULTS**

All 197 isolates tested were susceptible to moxifloxacin (MIC, <0.5 μg/mL), and up to 12.5% were resistant to the macrolides azithromycin and clarithromycin. Among macrolide-resistant strains, 2 distinct phenotypes were identified on the basis of MICs: high-level resistance (clarithromycin MIC, >256 μg/mL) was present in 3% of the isolates (24% of macrolide-resistant strains), and low-level resistance (clarithromycin MIC, 1.5–4 μg/mL) was evident in 76% of the resistant isolates. None of the resistant phenotypes showed a reduced susceptibility toward any other drug tested (table 1).

None of the isolates was resistant to β-lactams, although several strains (*n* = 10) showed a diminished susceptibility to penicillin (MIC, 0.25–0.75 μg/mL).

**DISCUSSION**

Despite the abuse of older fluoroquinolones in Mexico, none of the *S. pyogenes* isolates analyzed here showed diminished susceptibility toward moxifloxacin. The highest MIC recorded (0.5 μg/mL) is well below the moxifloxacin concentration in plasma and tissues as reported in pharmacokinetic studies [11] and below the proposed breakpoint for this drug (i.e., 1 μg/mL) [12] (figure 1). However, the observed level of macrolide resistance, at 12.5%, must be considered as cause for concern. Three different phenotypes have been distinguished for erythromycin-resistant strains of *S. pyogenes*: constitutive, inducible, and novel resistance phenotypes. The more recently recognized novel phenotype (M type) confers low- to medium-level resistance to erythromycin and other macrolides without affecting sensitivity to the macrolide-lincosamide-streptogramin B antibiotics. Thus, there is a significant level of cross-resistance between macrolides, and newer agents such as clarithromycin, azithromycin, and roxithromycin can be affected by it (figure 2).

The M type of resistance to macrolides, referred to above, has been shown to be an efflux pump conferred by the *mefA* gene,
which is found also in some strains of *S. pneumoniae*. Recent surveys have shown that the M type of resistance is the most prevalent form of macrolide resistance in several countries, including Austria, Italy, Spain, and the United States [3, 4].

Macrolide resistance is often accompanied by resistance to tetracyclines, and resistance to tetracyclines in *S. pyogenes* is widespread. It is often the highest in the strains with constitutive macrolide–lincosamide–streptogramin B resistance and more variable in the M phenotype strains.

In this study, the 90% MIC for penicillin was below the breakpoint of 0.12 μg/mL, but some strains had diminished susceptibility. In general, the penicillins remain uniformly highly active against *S. pyogenes*, and recent data indicate that the MICs of penicillin for group A streptococci have not changed in over 4 decades of use. Nevertheless, there have been a few reports of penicillin-tolerant strains developed in the laboratory. The clinical importance of these findings has yet to be determined. Of note in the present study is that all isolates of *S. pyogenes*, including the susceptible and resistant subpopulations, were susceptible to cefotaxime.

Regarding the resistance of *S. pyogenes* to macrolides and other antibacterials, the fact that strains intermediately resistant to penicillin do exist indicates the possibility of spread of additional modes of resistance to agents currently of high activity, as has happened with *S. pneumoniae*. The data presented here support the hypothesis that moxifloxacin may be an alternative choice in the treatment of pharyngotonsillitis caused by *S. pyogenes* when β-lactams are contraindicated. When a broad-spectrum antibiotic is needed and a β-lactam cannot be used, moxifloxacin offers a microbiologically more effective option than macrolides.

The activity of moxifloxacin against erythromycin-sensitive strains has been shown to be the same as erythromycin, but unlike erythromycin, moxifloxacin retained the same degree of activity against the strains displaying various types of erythromycin resistance [13]. In this same study, the rate and extent of kill was superior to ciprofloxacin. A rapid bactericidal effect is particularly important in *S. pyogenes* infections because the goal of antibiotic therapy is complete eradication of the microorganisms. As a final caveat, the possibility of cross-selection of fluoroquinolone-resistant gram-negative strains should be kept in mind when prescribing the newer fluoroquinolones.

References