Moxifloxacin, a New Antibiotic Designed to Treat Community-Acquired Respiratory Tract Infections: A Review of Microbiologic and Pharmacokinetic-Pharmacodynamic Characteristics

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Moxifloxacin (BAY 12-8039) is a new 8-methoxy-fluoroquinolone antibacterial agent. The minimum inhibitory concentration for 90% of organisms (MIC₉₀) is less than 0.25 mg/L for commonly isolated community-acquired respiratory tract pathogens including penicillin-susceptible and -resistant Streptococcus pneumoniae, Haemophilus sp, and Moraxella catarrhalis, and less than 1.0 mg/L for atypical pathogens such as Mycoplasma pneumoniae, Chlamydia pneumoniae, and Legionella pneumophila. To date, emergence of resistance to moxifloxacin has been uncommon, including selection of resistance under experimental conditions (methicillin-sensitive Staphylococcus aureus, S. pneumoniae). A postantibiotic effect is observed for both gram-positive and gram-negative bacteria. Human pharmacokinetics in healthy volunteers after a single 400-mg oral dose were mean maximum concentration (Cₘₐₓ) 3.2 mg/L, area under the curve (AUC) 37 mg•hour/L, and terminal elimination half-life 12.0 hours. At steady-state, Cₘₐₓ and AUC were approximately 4.5 mg/L and 48 mg•hour/L, respectively. Because of a balanced system of excretion, no dosage adjustments are required in patients with renal or hepatic impairment. Moxifloxacin also has excellent penetration into upper and lower respiratory tissues. Laboratory pharmacodynamic models suggest that MIC and AUC values predict therapeutic response. Notably, the drug can be administered once/day and is not associated with drug interactions secondary to altered hepatic metabolism. In addition, since its metabolism does not involve the cytochrome P450 system, many common drug interactions are absent. The agent is being investigated in clinical trials and shows promise as a safe and effective once-daily treatment of respiratory infections. In addition, its chemical structure and pharmacokinetic and pharmacodynamic properties indicate that it has enhanced potential to minimize emergence of bacterial resistance, which should make it an excellent choice for treating respiratory tract infections now and in the future.

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Summary

Fluoroquinolones with systemic activity have been available for clinical use in the United States since 1987. Each currently available drug in this class has distinct microbiologic, pharmacokinetic, pharmacodynamic, and safety profiles. The older systemic quinolones (e.g., ciprofloxacin, ofloxacin) are characterized by broad-spectrum antibacterial in vitro activity, although borderline susceptibility and emerging resistance to some organisms were reported, especially for respiratory tract pathogens.1-3 In general, for older positive organisms is not as potent as activity against gram-negative bacteria.4 To address these limitations, research efforts focused on modifying the quinolone molecule. Several newer agents (e.g., moxifloxacin, gatifloxacin), which became available in the late 1990s, appear to be valuable alternatives for patients with gram-positive or gram-negative respiratory tract infections.

Community-acquired respiratory tract infections, such as sinusitis, acute exacerbations of chronic bronchitis, and pneumonia, are increasingly common and are in part responsible for escalating health care costs.5 These infections are often bacterial, caused by Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis, Klebsiella pneumoniae, and Staphylococcus aureus and atypical pathogens such as Chlamydia pneumoniae, Mycoplasma pneumoniae, and Legionella pneumophila. Rapid and increasing resistance to commonly administered macrolide, β-lactam, and penicillin antimicrobials by some of these pathogens has been reported.5-10

Resistance among these organisms in the United States rose dramatically over the past 2 decades, with β-lactamase production evident in approximately 40% of H. influenzae and more than 95% of M. catarrhalis isolates.6-8 In addition, almost 20% of pneumococci are highly resistant to penicillin and simultaneously resistant to other β-lactam and macrolide antibiotics;6-9 43.8% of S. pneumoniae strains isolated from patients in the United States with respiratory tract infections during 1997 were resistant to penicillin (27.8% intermediate, 16% high-level resistance).9 Another survey during the 1996-1997 respiratory season reported a significant rise in resistance levels, as approximately 34% of 9190 isolates of S. pneumoniae were penicillin resistant.10 Many of these resistant strains showed intermediate or high-level resistance to β-lactams and macrolides, including amoxicillin-clavulanate, cefuroxime, ceftriaxone, and clarithromycin.10 In contrast, fluoroquinolones are very active against all pneumococcal isolates, independent of penicillin susceptibility.10,11 However, some of the older fluoroquinolones have only borderline activity against some isolates of S. pneumoniae, Streptococcus sp, and S. aureus.1-4

The cited resistance rates were for hospital-acquired pathogens. The exact prevalence of resistant organisms in the community remains to be determined. In addition, reporting of resistance is based mainly on hospital-acquired pathogens. Resistance reporting, which is based on breakpoints and not on a drug's ability to cure an infection in patients, may or may not reflect clinical management problems, and reporting of resistance in hospital-acquired pathogens may or may not apply to treatment of respiratory infections in the community (out of hospital setting).

Rapid and increasing development of resistance of community-acquired respiratory tract pathogens to conventional antimicrobials suggests that some geographic locations may require different treatment strategies. An ideal new antimicrobial for treating these infections should have activity against all predominant respiratory pathogens, including the growing number of resistant organisms; have rapid killing; have low potential for inducing resistance; have optimal pharmacokinetic and pharmacodynamic profiles; show excellent tissue penetration; have an acceptable safety profile; and produce high clinical response rates. Several newer fluoroquinolones with enhanced gram-positive activity, including grepafloxacin, trovafloxacin, moxifloxacin, and gatifloxacin, have received approval...
from the Food and Drug Administration or are under review for the treatment of selected respiratory tract infections.

Although moxifloxacin (BAY 12-8039) has activity against a broad range of pathogens and may be effective in treating infections outside the respiratory tract, it was designed to be a “respiratory” drug. Most patients treated with moxifloxacin have had underlying upper or lower respiratory tract infections.

Chemistry

Moxifloxacin, an 8-methoxyquinolone, was synthesized by Bayer AG (Leverkusen, Germany) and has the chemical structure 1-cyclopropyl-7-[(S,S)-2,8-diazabicyclo[(4.3.0)]-non-8-yl]-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinoline carboxylic acid hydrochloride. Moxifloxacin has enhanced antibacterial activity due to a cyclopropyl group at N-1 and a fluorine at C-6.12,13 An azabicyclo-substitution at C-7 is associated with substantially improved gram-positive activity. Of additional importance, in studies of S. aureus, the presence of a methoxy group at the C-8 position was associated with a decreased propensity for development of resistance (see section on emergence of resistance).14 In particular, the potential ability of moxifloxacin to kill first-step resistant mutants may greatly reduce the ability of wild-type populations to acquire resistance. Fluoroquinolones with C-8 halogenation are associated with moderate to severe phototoxicity (e.g., sparfloxacin). With moxifloxacin, this was circumvented by substituting a C-8 methoxy group.

The proper dosing of antimicrobials results in effective bacterial eradication and suppression of resistance. This is based on a drug’s pharmacodynamic properties, which index microbiologic activity to achievable drug concentrations. Therefore, both microbiologic and pharmacokinetic properties must be evaluated simultaneously.

In Vitro Activity

Moxifloxacin has potent antibacterial activity against a broad range of commonly encountered respiratory tract pathogens including gram-positive, gram-negative, and atypical bacteria (Table 1).15–22 In addition, it has excellent in vitro activity against anaerobes.23, 24 Its aerob activity against respiratory tract bacteria is based on the minimum concentration necessary to inhibit 90% of strains (MIC90).

Gram-Positive Bacteria

Streptococcus pneumoniae

Unlike older fluoroquinolones, moxifloxacin has excellent in vitro activity against S. pneumoniae.15–17, 21, 25–29 Among these reports, the agent’s MIC90 against the pneumococcus was 0.25 mg/L (range 0.06–0.5 mg/L).15–17, 21, 25–29

Most reports found no difference in the in vitro activity of moxifloxacin against penicillin-susceptible or penicillin-resistant isolates.21, 27, 29 However, a small difference was seen in in vitro activity against penicillin-susceptible (0.06 mg/L) versus penicillin-resistant organisms (0.125 mg/L).26 The drug had 2-fold greater activity against ciprofloxacin-susceptible strains compared with ciprofloxacin-resistant strains.16

Moxifloxacin is more active in vitro against S. pneumoniae than ciprofloxacin, ofloxacin, levofloxacin, lomefloxacin, and grepafloxacin.16, 17, 21, 26, 27 but has comparable activity as trovafloxacin and gatifloxacin.16, 30 Moxifloxacin and trovafloxacin had at least 8-fold greater activity against 452 clinical isolates of that organism than ciprofloxacin and levofloxacin.31 Furthermore, the in vitro activity of moxifloxacin against pneumococci, especially penicillin-resistant isolates, was greater than that of newer macrolides (azithromycin, clarithromycin), amoxicillin-clavulanate, and oral β-lactams (e.g., cefuroxime).16, 26–28

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### Table 1. In Vitro Susceptibility: Comparative MIC90 Against Bacterial Respiratory Pathogens for Selected Newer Fluoroquinolones

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Moxifloxacin</th>
<th>Levofloxacin</th>
<th>Trovafloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemophilus influenza</td>
<td>0.06</td>
<td>0.06</td>
<td>0.016</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
<td>0.03</td>
<td>0.03</td>
<td>0.015-0.03</td>
</tr>
<tr>
<td>Strep. pneumoniae</td>
<td>0.06-0.25</td>
<td>1.0-3.13</td>
<td>0.12-0.5</td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td>0.06-0.12</td>
<td>—</td>
<td>0.06-0.25</td>
</tr>
<tr>
<td>Legionella pneumophilia</td>
<td>0.015</td>
<td>0.032</td>
<td>0.12-0.5</td>
</tr>
<tr>
<td>Chlamydia pneumoniae</td>
<td>0.03-1.0</td>
<td>0.25-0.5</td>
<td></td>
</tr>
</tbody>
</table>

*Includes some β-lactamase-producing isolates.

*Values represent MIC90 against Legionella sp, not L. pneumophila specifically.

*Values represent MIC90 against Chlamydia sp, not C. pneumoniae specifically.
Streptococcus aureus

Moxifloxacin’s activity against both methicillin-susceptible and -resistant isolates was studied. Against methicillin-susceptible *S. aureus*, the agent’s MIC₉₀ ranged from 0.06–0.125 mg/L.¹⁵–¹⁷, ²⁸, ²⁹ For methicillin-resistant *S. aureus* (MRSA), the drug’s activity lessens, with MIC₉₀ from 1–8 mg/L.¹⁵–¹⁷, ²⁸, ²⁹ Notably, its activity is less for strains that are both methicillin and ciprofloxacin resistant compared with those that are methicillin susceptible.¹⁵, ¹⁶ Despite that moxifloxacin has less activity in vitro against MRSA, it still has 4- to 8-fold better in vitro activity (4- to 8-fold lower MICs) than ciprofloxacin, ofloxacin, and levofloxacin.¹⁵, ²⁹

Gram-Negative Bacteria

*Haemophilus* Species

Moxifloxacin has excellent activity against both β-lactamase-negative and -positive isolates of *H. influenzae*, with most isolates having MIC₉₀s from 0.03–0.06 mg/L.¹⁵–¹⁷, ²¹, ²⁶, ²⁸, ²⁹ Occasional isolates had MIC₉₀s of 0.125 mg/L.¹⁵, ²⁻¹⁷, ²⁹ In these studies, moxifloxacin was approximately 2- to 4-fold less active than ciprofloxacin, ofloxacin, and levofloxacin. It is also 2- to 4-fold less active for *H. influenzae* than trovafloxacin.¹⁶, ¹⁷, ²¹ Compared with amoxicillin-clavulanate, cefuroxime, and clarithromycin, moxifloxacin had greater activity against both β-lactamase-negative and -positive *H. influenzae*.²⁸

The agent also had excellent in vitro activity for *H. parainfluenzae*, an increasingly recognized pathogen in respiratory tract infections, with MIC₉₀s from 0.03–0.25 mg/L.¹⁷, ³² In one study, it had lower MIC₉₀s (0.25 mg/L) than cefuroxime (4.0 mg/L), amoxicillin-clavulanate (8.0 mg/L), clarithromycin (16.0 mg/L; the active metabolite of clarithromycin was not studied, therefore the MIC₉₀ against that drug may be overstated), and azithromycin (2.0 mg/L).³²

*Moraxella catarrhalis*

Similar to *Haemophilus* sp, moxifloxacin has excellent activity against *M. catarrhalis* with MIC₉₀ from 0.03–0.125 mg/L.¹⁶, ¹⁷, ²¹, ²⁵, ²⁶, ²⁹ Its activity is not compromised in the presence of β-lactamase.¹⁷, ²⁹ It has similar activity as older fluoroquinolones, as well as levofloxacin and trovafloxacin.¹⁶, ¹⁷, ²¹ Compared with amoxicillin-clavulanate, cefuroxime, loracarbef, and clarithromycin, it had substantially lower MIC₉₀s against β-lactamase-producing isolates (4- to 66-fold lower).²⁸

*Klebsiella pneumoniae*

The average MIC₉₀ for moxifloxacin against *K. pneumoniae* is 0.125 mg/L for ceftazidime-sensitive strains, compared with 8 mg/L for ceftazidime-resistant strains.¹⁷ However, for ceftazidime-resistant strains, all tested fluoroquinolones had substantially higher MIC₉₀s, including trovafloxacin (16 mg/L).¹⁷ In another trial, moxifloxacin had an MIC₉₀ of 1 mg/L for strains isolated from patients in intensive care units.²⁸

Atypical Bacteria

*Moraxella pneumoniae*, *C. pneumoniae*, and *L. pneumophila* are increasingly common causes of respiratory tract infections, especially community-acquired pneumonia. At least two studies reported an average MIC₉₀ for moxifloxacin of 0.125 mg/L against *M. pneumoniae*.²⁰, ³³ Similar or slightly less activity was reported for doxycycline and clarithromycin.²⁰ However, moxifloxacin had greater in vitro activity than ofloxacin, grepafloxacin, and trovafloxacin.³³

The MIC₉₀s for moxifloxacin against *C. pneumoniae* were 0.03–1.0 mg/L, with 0.125 mg/L for most strains.¹⁶, ¹⁸, ³⁴, ³⁵ Against 23 strains the MIC₉₀ was 0.5 mg/L for grepafloxacin,³⁶ and against 12 strains it was 1.0 mg/L for trovafloxacin.³⁷

The activity of moxifloxacin against 12 strains of *L. pneumophila* was similar to that of ciprofloxacin and levofloxacin, with a range of 0.015–0.06 mg/L.³⁸ Moxifloxacin’s MIC₉₀ against 30 clinical isolates of *Legionella*, including 21 *L. pneumophila*, was 0.06 mg/L using noncharcoal-containing media.³⁹

Pharmacokinetic Properties

Activity as measured by MIC must be evaluated based on achievable drug concentrations in blood and tissue.⁴⁰–⁴² In this regard, clinical and bacteriologic outcomes are believed to be related in part to the time the serum concentration exceeds the MIC or the ratio of plasma area under the curve (AUC) to MIC.⁴³ The pharmacokinetics of oral moxifloxacin were studied after single doses 50–800 mg and in several dosages of up to 600 mg once/day for 10 days. In general, the pharmacokinetics were linear for all regimens. Because the agent’s recommended dosage will be 400 mg once/day
orally, this discussion focuses primarily on the pharmacokinetics with this dosage. Although pharmacokinetic and clinical investigations with an intravenous formulation recently began, data are not available for summary.

Clinical Pharmacokinetics

The pharmacokinetics of moxifloxacin were investigated with 400 mg as a single dose or once/day for up to 10 days. In healthy volunteers, the mean maximum serum concentration (Cmax) after a single dose ranged from 2.5 mg/L to 3.4 mg/L and was reached within 1.5 hours. Corresponding AUC values on day 1 were 26–37 mg•hour/L. In a multiple-dose study, mean steady-state Cmax and AUC on day 10 were 4.5 mg/L and 48 mg•hour/L, respectively. The mean accumulation ratio (AUCss:AUC0–∞, Day 1) was approximately 1.6 on day 10. Twenty-four hours after the tenth dose the mean trough serum concentration was approximately 1.0 mg/L, which exceeds the MIC for most common respiratory tract pathogens.

Moxifloxacin's elimination half-life is approximately 12 hours (range 10–16 hrs). This and the low MIC against potential pathogens support once/day dosing. Table 2 summarizes the clinical pharmacokinetics of moxifloxacin 400 mg compared with other fluoroquinolones.

Distribution and Respiratory Tissue Penetration

Moxifloxacin is not highly protein bound, with an approximate 48% affinity to plasma proteins; the extent of protein binding remained constant regardless of the plasma concentration. The volume of distribution is estimated to be 3.6 L/kg, suggesting good distribution to tissue compartments. When measured 24 hours after a single oral dose of 400 mg, unbound concentrations in skin blister fluid were 1.5 times higher than serum concentrations.

Several studies documented the drug's penetration into respiratory tract tissues (Table 3). Concentrations were higher in epithelial lining fluid and bronchial tissue than in plasma. In 18 patients who received a single 400-mg dose before routine bronchoscopy, mean epithelial lining fluid concentrations were 24.4 mg/L 1 hour after the dose; tissue:serum ratios ranged from 6.6–7.4 over 3–24 hours. Corresponding mean concentrations in bronchial tissue were 5.5 mg/L, with tissue:serum ratios approximating 2:1 over the same time. In addition, moxifloxacin was highly concentrated in macrophages (113.6 mg/L 12 hrs after the dose), whereas levofloxacin and trovafloxacin concentrated 3- to 6-fold less (41.9 and 19.1 mg/L, respectively). Moxifloxacin's sinus concentrations were measured in 34 patients with chronic sinusitis who received five doses of 400 mg once/day orally before surgery. Levels in maxillary sinus mucosa were higher.

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Table 2. Steady-State Pharmacokinetic Properties of Newer Fluoroquinolones after Several Oral Doses

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Levofloxacin</th>
<th>Trovafloxacin</th>
<th>Moxifloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg/day)</td>
<td>500</td>
<td>200</td>
<td>400</td>
</tr>
<tr>
<td>Cmax (mg/L)</td>
<td>5.7</td>
<td>3.1</td>
<td>4.5</td>
</tr>
<tr>
<td>AUC (mg•hr/L)</td>
<td>48.0</td>
<td>34.4</td>
<td>48.0</td>
</tr>
<tr>
<td>Half-life (hrs)</td>
<td>7.6</td>
<td>12.0</td>
<td>12.0</td>
</tr>
<tr>
<td>Major route(s) of elimination</td>
<td>Renal</td>
<td>Hepatic</td>
<td>Renal, hepatic</td>
</tr>
</tbody>
</table>

Table 3. Respiratory Tract Tissue, Fluid Penetration of New Oral Fluoroquinolones

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Sample Time</th>
<th>Plasma Concentration (mg/L)</th>
<th>Lung Concentrations (mg/kg or mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bronchial Mucosa</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>Peak</td>
<td>2.5–5.0</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td>Trough</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Trovafloxacin</td>
<td>Peak</td>
<td>1.4–2.2</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>Trough</td>
<td>0.4</td>
<td>ND</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Peak</td>
<td>6.6</td>
<td>8.3</td>
</tr>
<tr>
<td></td>
<td>Trough</td>
<td>1.2</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND = not detectable.
than those in plasma, with peak sinus concentrations (7.5 mg/kg) 3 hours after the dose. At 36 hours after the dose, sinus levels were 1.25 mg/kg. Similar concentrations were measured in anterior ethmoid mucosa and nasal polyp tissue.

Based on available data, bronchial mucosa and epithelial lining fluid concentrations of moxifloxacin appear to be much higher and stay higher over the entire 24-hour dosing interval than MICs reported for commonly isolated respiratory tract pathogens including S. pneumoniae, H. influenzae, and M. catarrhalis. Intracellular concentrations also appear to be sufficient to inhibit atypical pathogens.49

Metabolism and Elimination

Moxifloxacin is excreted by both hepatic and renal routes, as evidenced by total clearance values of 14.9 and 3.0 L/hour, respectively.45 The drug's principal metabolites in humans are N-sulfate and acyl-glucuronide conjugates.53 Approximately 22% of intravenously administered moxifloxacin is eliminated unchanged, 14% as the glucuronide and 2.5% as the N-sulfate by the renal pathway.45, 53, 54 Approximately 26% of an intravenous dose is excreted in feces as unchanged drug and an additional 34% as the sulfate metabolite.53, 54 Although moxifloxacin is eliminated in part by renal mechanisms, renal impairment does not significantly affect its oral clearance.55 In 32 volunteers with various degrees of renal dysfunction (creatinine clearance < 1.8 to > 5.4 L/hr/1.73 m²) who received a single dose of 400 mg, renal clearance decreased, but no dosage reduction was necessary. In addition, the N-sulfate and acyl-glucuronide metabolites did not accumulate to any significant extent. No investigations of the drug have been performed in patients undergoing dialysis.

Potential effects of hepatic impairment on a single dose moxifloxacin 400 mg were studied in 8 patients categorized with Child-Pugh class A or B hepatic disease and compared with 10 healthy age-matched volunteers.56 Mean AUC estimates were 25.1 and 32.8 mg•hour/L, respectively, elimination half-life values were 11.7 and 13.4 hours, respectively, and mean apparent total body clearance values were 16 and 12.2 L/hour, respectively. The drug was not associated with serious or significant adverse events or premature discontinuation in patients with mild to moderate hepatic dysfunction. The authors concluded that no dosage adjustments are required for moxifloxacin in these patients.

Age and Gender Effects

To determine whether age or gender influenced the pharmacokinetics of this drug, a double-blind study was conducted in which 36 healthy volunteers received either a single oral dose of moxifloxacin 200 mg or placebo.57 The groups of 12 (8 active drug, 4 placebo) included young men (mean age 32 yrs), elderly men (mean age 74 yrs), and elderly women (mean age 74 yrs). Although C_{max} and AUC were higher in elderly women (1.95 mg/L, 25.2 mg•hour/L) than in elderly men (1.6 mg/L, 19.9 mg•hour/L) and young men (1.35 mg/L, 19.1 mg•hour/L), the differences were not clinically significant after correction for body weight. Elimination half-life averaged 12 hours for all three groups. In summary, no important age and gender differences in pharmacokinetics occurred after single doses of the agent.

Drug Interaction Studies

Food and Dairy Effects

The effects of a high-fat breakfast on the pharmacokinetics of a single oral dose of moxifloxacin 400 mg were investigated in a randomized, two-way, nonblinded, crossover study in 16 healthy young men.58 The AUCs under fed and fasted conditions were nearly identical, 37.8 and 38.5 mg•hour/L, respectively. The only consistent effect of food was that the drug's absorption was slightly delayed (geometric mean time to C_{max} [T_{max}] 1.0 and 2.5 hrs, fasting and fed conditions, respectively). These data suggest that moxifloxacin may be taken with or without food.

Administration of yogurt with a single 400-mg moxifloxacin dose had no significant effect on overall bioavailability (AUC 33.9 mg•hr/L without vs 31.8 mg•hr/L with yogurt).59 However, T_{max} was delayed in the presence of yogurt (0.9 hr without vs 2.75 hrs with yogurt). The C_{max} was reduced slightly (15%) after consumption of yogurt. These changes are not considered clinically significant and therefore do not warrant changes in dosage.

Metal Cation-Containing Agents

Similar to other fluoroquinolones, the bioavailability of moxifloxacin is significantly reduced in the presence of multivalent metal cations. When moxifloxacin 400 mg was given concomitantly with Maalox 3 times/day, AUC and C_{max} decreased 45% and 40%, respectively.60 The
agent's bioavailability, however, was unaffected if the antacid was given 2 hours before or 4 hours after the quinolone. This result is consistent with other fluoroquinolones and is considered to be a class effect.

Coadministration of ferrous sulfate with moxifloxacin also affected the absorption of the quinolone. Both C\text{max} and AUC were lower after simultaneous administration (1.2 mg/L, 20.7 mg*hr/L) compared with when moxifloxacin was given alone (2.9 mg/L, 34.0 mg*hr/L). The rate of absorption (T\text{max}) also was delayed by approximately 60% when ferrous sulfate was given with moxifloxacin. These findings suggest that, to preserve moxifloxacin's therapeutic effect, it should not be coadministered with iron-containing products.

Probenecid, Theophylline, Histamine\textsubscript{2}-Receptor Antagonists, and Anticoagulants

Unlike ciprofloxacin, the renal clearance of moxifloxacin after a single 400-mg dose was unaffected by coadministration of four doses of probenecid 500 mg. Of importance, moxifloxacin is not reported to have clinically relevant interactions with theophylline, ranitidine, or warfarin.

Moxifloxacin 200 mg twice/day and theophylline 400 mg twice/day, each given alone and in combination, were administered to 12 healthy volunteers. The pharmacokinetics of neither agent were significantly altered after coadministration, after a single dose, or at steady state. Because moxifloxacin is not metabolized by the cytochrome P450 system, lack of an interaction was not unexpected. Among newer fluoroquinolones, only grepafloxacin significantly reduces theophylline clearance by almost 50%.

Twelve healthy male volunteers received a single oral 400-mg dose of moxifloxacin either alone or concomitantly with ranitidine 150 mg twice/day after administration of the histamine\textsubscript{2} (H\textsubscript{2})-receptor antagonist for 3 days. Ranitidine had minimal effect on overall bioavailability, elimination half-life, and urinary excretion of moxifloxacin.

In healthy volunteers, moxifloxacin 400 mg once/day for 8 days had no significant effect on the pharmacokinetics or pharmacodynamics of warfarin after a single 25-mg dose. In addition, the pharmacokinetics of moxifloxacin were not altered with warfarin.

Pharmacodynamic Properties

Although MICs and pharmacokinetic properties of an antimicrobial may provide a clue to a patient's therapeutic outcome, either one alone is not a sufficient predictor of clinical response. Accordingly, pharmacodynamic evaluations are used to predict in vivo activity. Antimicrobials often are divided into pharmacodynamic classes based on whether their in vivo effects are concentration dependent (e.g., fluoroquinolones, aminoglycosides) or predominantly concentration independent (e.g., \(\beta\)-lactams, macrolides). The pharmacodynamic properties of moxifloxacin were predicted by performing in vitro time-kill kinetic studies and by examining postantibiotic effect (PAE). Time-kill curves reflect bactericidal activity, which is expressed as the rate of killing by a fixed concentration of the agent against a bacterium with a specific MIC. The PAE is defined as continued suppression of an organism's growth after short exposure to an antimicrobial and often is considered to be significant if greater than 1 hour.

Time-Kill Studies

Similar to other fluoroquinolones, moxifloxacin has bactericidal activity, shown by minimum bactericidal concentrations that are equal to or within one tube dilution of the MIC. Several studies confirmed this activity against both gram-positive and gram-negative respiratory tract organisms. The time-kill kinetics of moxifloxacin were studied against \(S\). \textit{aureus}, \(H\). \textit{influenzae}, and \(S\). \textit{pneumoniae} at two inocula, 10\textsuperscript{5} and 10\textsuperscript{7} colony-forming units/ml, with drug concentrations ranging from 1–10 x MIC. Although bactericidal activity was noted for all organisms tested, the effect was most rapid against \(S\). \textit{aureus}. Killing for \(S\). \textit{aureus} occurred within 2.5 hours and against \(S\). \textit{pneumoniae} within 3.5 hours. In one study, time-kill kinetics for \(\beta\)-lactamase-producing \(H\). \textit{influenzae} indicated that moxifloxacin had greater bactericidal activity than cefuroxime, cefprozil, and ampicillin-sulbactam. Its bactericidal activity against methicillin-susceptible and -resistant \(S\). \textit{aureus} and \(S\). \textit{pneumoniae} was superior to that of comparative agents.

Time-kill experiments also were conducted using variable concentrations to simulate human serum concentrations after oral administration. Simulated moxifloxacin concentrations after a single 400-mg dose showed steady killing of \(S\). \textit{pneumoniae}, \(H\). \textit{influenzae}, and \(M\). \textit{catarrhalis}. Specifically, \(S\). \textit{pneumoniae} isolates, regardless of antibiotic susceptibility or resistance, were killed...
rapidly with maximum reduction of 4.5–5.5 log_{10} after 24 hours of drug exposure. Gram-negative isolates were killed even more rapidly, with a 5.5 log reduction within 4 hours of exposure. None of the organisms tested exhibited regrowth within the 24-hour period. Findings were similar using peak concentrations achieved by moxifloxacin 400 mg against S. pneumoniae strains (MIC 0.25 mg/L). Then, Gram-negative isolates were killed even more rapidly, with a 5.5 log reduction within 4 hours of exposure. None of the organisms tested exhibited regrowth within the 24-hour period. Findings were similar using peak concentrations achieved by moxifloxacin 400 mg against S. pneumoniae strains (MIC 0.25 mg/L).72

Overall, time-kill studies against a variety of respiratory organisms show that the drug exhibits concentration-dependent killing.15, 26, 69–75 Of interest, it also exhibits time-dependent killing (greater killing at 5 vs 4 hrs after exposure), probably related to its activity at lower concentrations.74 In summary, moxifloxacin is bactericidal against common respiratory tract bacteria, including penicillin-resistant S. pneumoniae and gram-positive organisms that are either β-lactam or vancomycin resistant.76

Postantibiotic Effect
Moxifloxacin's PAE was studied after exposure to a variety of organisms.69 Using drug concentrations that were 4 and 10 x MICs, several respiratory pathogens were associated with a significant PAE, including S. pneumoniae (1.2–2.9 hrs), H. influenzae (1.2–3.1 hrs), and S. aureus (1.4–3.1 hrs).69 Similar preliminary findings were reported in at least two other studies.75, 77 The PAE effect did not differ between penicillin-susceptible and -resistant strains.78

Similar to other fluoroquinolones, the PAE of moxifloxacin is prolonged with increasing concentrations.69, 75, 77 Although the clinical significance of PAE is debated, for this agent it is 1–6 hours, depending on the bacteria.

C_{max}:MIC and AUC:MIC Ratios
A C_{max}:MIC ratio greater than 10 is a strong predictor of clinical success.79 However, whereas it is considered optimal, it does not mean that patients with lower ratios will be clinical failures. Moxifloxacin had a higher C_{max}:MIC ratio (10–80) than levofloxacin (2–13) and sparfloxacin (1–10) against S. pneumoniae isolates.80 This suggests that moxifloxacin has bactericidal activity, and that based on these ratios, S. pneumoniae theoretically is less likely to develop resistance to moxifloxacin than to the other fluoroquinolones.

The AUC:MIC_{90} ratios over 24 hours are also predictive of clinical response to fluoroquinolones.43, 81 The probability of clinical cure of infection with gram-negative organisms often was correlated with ratios above 125. For gram-positive organisms, ratios greater than 30 are considered to predict success, especially for S. pneumoniae.82

Emergence of Resistance
The development of resistance is the same issue that is involved in eradicating bacteria, except from the opposite perspective. Resistance develops when bacteria are exposed to antimicrobials but are not killed.

Although it long has been appreciated that quinolones are extremely potent with the ability to trap DNA gyrase on DNA, it only recently was established that DNA topoisomerase IV is also a target of this class of drugs.83 Some bacteria (e.g., S. aureus) easily acquire resistance mutations, thereby limiting the usefulness of some fluoroquinolones.83 Accordingly, growing recognition of multiantibiotic-resistant bacteria stimulated the search for new tactics to minimize the emergence of mutant isolates. Topoisomerase-based resistance to fluoroquinolones occurs as a stepwise process. The first-step mutation occurs as a single mutation in the primary target of the quinolone (gyrase or topoisomerase IV, depending on the bacterial species). This mutation results in a moderate degree of resistance. The second-step mutation leads to a higher degree of resistance resulting from further mutations in both primary and secondary enzyme targets. Based on this understanding, the availability of an antimicrobial that fervently would attack a resistant, first-step mutant would be ideal. As such, the bacterium would have to acquire two topoisomerase mutations to express resistance and render the drug ineffective. A bacterium that could do this would occur at a much lower frequency than a bacterium with one mutation. Sophisticated research has established that C-8-methoxy fluoroquinolones, such as moxifloxacin, require two mutations for expression of resistance.
resistance. Addition of a C-8-methoxy group to an N-1-cyclopropyl fluoroquinolone lowers the concentration required to prevent mutants from being recovered—the mutant prevention concentration.

Development of resistance of respiratory pathogens to antimicrobial agents escalated in the past decade, most notably for macrolides, penicillins, and other β-lactam agents. So far, the propensity for development of resistance to moxifloxacin by the gram-positive cocci, S. aureus and S. pneumoniae, has been uncommon. For example, for S. pneumoniae the mutation rate for resistance to moxifloxacin was low (<1.4 × 10⁻⁹). Furthermore, moxifloxacin resistance was uncommon when quinolone-containing media were used. In a second in vitro study of S. pneumoniae, moxifloxacin was less likely than ciprofloxacin to select mutants with reduced susceptibility. Both studies found moxifloxacin to be at least 10-fold less likely than either ciprofloxacin or ofloxacin to select mutant strains of these pathogens.

The frequency of development of spontaneous resistance to moxifloxacin was 2.5 × 10⁻⁷ to < 4 × 10⁻⁸ when methicillin-susceptible and -resistant isolates of S. aureus, M. catarrhalis, and S. pyogenes were exposed to drug concentrations at 8 × MIC. Using concentrations at 8 × MIC, S. aureus mutants rarely were selected with moxifloxacin (4 × 10⁻⁸ to < 5.6 × 10⁻⁹). Similar to most other fluoroquinolones, the target for moxifloxacin in S. aureus appears to be topoisomerase IV. In another report, the agent's activity minimally was affected by mutations affecting grlA, grlB, gyrA, and gyrB loci in S. aureus isolates. Furthermore, moxifloxacin was the least affected of five fluoroquinolones (ciprofloxacin, ofloxacin, levofloxacin, sparfloxacin) tested.

These studies suggest that this drug appears to have a low propensity to induce resistance compared with other fluoroquinolones. Because it can eradicate bacteria that undergo first-step mutation, it has a distinct advantage over the older fluoroquinolones, which cannot eradicate these isolates.

Summary

In this era of emerging resistance of community-acquired respiratory pathogens to cephalosporins and other β-lactams, macrolides, and tetracyclines, it is notable that moxifloxacin has excellent in vitro inhibitory activity against antibiotic-resistant S. pneumoniae, β-lactamase-producing Haemophilus sp, and M. catarrhalis, as well as atypical organisms. It also has an excellent pharmacokinetic profile characterized by respiratory tissue concentrations that significantly exceed serum levels, and a long elimination half-life that permits once-daily dosing. The excellent pharmacodynamic profile implies that the drug can achieve high response rates with shorter courses of therapy while minimizing the development of resistance.

Compared with older systemic and some recently marketed fluoroquinolones, moxifloxacin is not associated with clinically significant drug interactions due to inhibition or stimulation of hepatic metabolism (e.g., theophylline). Thus it does not require special clinical or laboratory monitoring to ensure its safety. Agents that do not require additional monitoring decrease the cost of care and prevent unnecessary hospitalization and inconvenience to the patient.

Although beyond the scope of this review, results of well-designed, prospective, and comparative clinical trials conducted in the United States proved moxifloxacin to be safe and efficacious in treating community-acquired sinusitis, acute exacerbations of chronic bronchitis, and pneumonia. The agent's safety and tolerability were summarized by meta-analysis of over 4300 patients. As with other fluoroquinolones, the most frequently reported drug-related events attributable to moxifloxacin were nausea, diarrhea, and dizziness. Premature discontinuation was less than 1%. Although a minimal prolongation of the QTc interval was observed after administration of moxifloxacin (mean increase 4 msec), this finding was similar to other antibiotic comparators, including clarithromycin, and was not associated with clinical adverse events. In this analysis of 20 phase III trials, moxifloxacin was not associated with significant changes in hepatic function and appeared to have low photosensitizing potential. Preliminary data suggest that a dosage of 400 mg once/day orally appears to be a safe and well-tolerated alternative for empiric and organism-specific therapy for patients with community-acquired respiratory tract infections.

References

3. Piddock LJV. Fluoroquinolone resistance. BMJ 1998;317:


Stass HH, Kubitzra D. Mass balance and excretion patterns for moxifloxacin in man following single 400 mg oral and intravenous doses [abstr]. Presented at the 8th International Conference of Infectious Diseases, Boston, May 15–18, 1998.


Stass HH, Kubitzra D. Study to assess the interaction between moxifloxacin and dairy products in healthy volunteers [abstr].

Anti-Infect Drug Chemother 1998;16(suppl 1):74.

Stass HH, Boetcher M, Horstmann R. Study to evaluate the interaction between BAY 12-8039 (BA) and antacids (AN) [abstr]. Presented at the 20th International Congress of Chemotherapy, Sydney, Australia, June 29–July 3, 1997.

Stass H, Kubitzra D. Study to evaluate the interaction between moxifloxacin (M) and iron supplements (FE) [abstr]. Presented at the 2nd European Congress of Chemotherapy and 7th Biennial Conference on Anti-infective Agents and Chemotherapy, Hamburg, Germany, May 10–13, 1998.


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