Fluoroquinolone drug class update

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The approval of trovafloxacin (Trovan, Pfizer Pharmaceuticals, New York, NY) by the Food and Drug Administration (FDA) in 1998 was met with great excitement by many clinicians based on its utility as monotherapy for numerous indications. In comparison with other available fluoroquinolones, trovafloxacin offered enhanced activity against anaerobic and gram-positive organisms, including *Streptococcus pneumoniae*. In June 1999 the FDA made a formal statement outlining recommendations for the cautious use of trovafloxacin in specific patient populations. Postmarketing experience revealed several cases of liver toxicity associated with the use of trovafloxacin, although similar findings had not been documented in earlier studies. The experience magnified the limitations of information gained through clinical trials. Often the true profile of a drug is discovered after it is used on thousands of patients. Therefore, we must review new drug literature with some degree of skepticism, especially when safety and efficacy trials have been performed with healthy volunteers.

When the latest fluoroquinolone agents, gatifloxacin (Tequin, Bristol-Myers Squibb, Princeton, NJ) and moxifloxacin (Avelox, Bayer Corporation, West Haven, Conn), were released, the postmarketing toxicities experienced with trovafloxacin became even more relevant. The following review highlights the clinical data available for the 2 new agents.

GATIFLOXACIN

The FDA approved gatifloxacin, an advanced-generation fluoroquinolone, in December 1999 for the treatment of community-acquired pneumonia, acute sinusitis, acute bacterial exacerbation of chronic bronchitis, uncomplicated skin and skin structure infections, uncomplicated and complicated urinary tract infections, and pyelonephritis. It was also approved for uncomplicated urethral, pharyngeal, and rectal gonorrhea in men and for endocervical, pharyngeal, and rectal gonorrhea in women. Gatifloxacin is entering the market as an agent that is expected to be comparable to levofloxacin and is touted to have pharmacologic properties that may provide a more favorable side effect profile and improved activity against resistant organisms.

Pharmacology/pharmacokinetics

Gatifloxacin has a unique chemical structure with key functional groups that may improve its side effect profile and reduce its potential for developing bacterial resistance. The most distinct difference between gatifloxacin's structure and those of other

fluoroquinolones is the 8-methoxy group at position 8. It is believed that this group mediates the binding of the DNA–DNA gyrase complex to the DNA-topoisomerase complex and potentially decreases the likelihood of high-level resistance. The lack of halogenation at position 8 indicates that gatifloxacin, like ciprofloxacin and levofloxacin, may decrease a patient's risk of developing phototoxicity. Other side effects that are associated with the fluoroquinolones are believed to be influenced by substitutions at the R7 position. Gatifloxacin's chemical structure at this R7 position includes a methyl-substituted piperazinyl ring, which has the potential to decrease the risk associated with non-steroidal anti-inflammatory drug interactions, central nervous system toxicity, and genotoxicity (1–3).

Characteristic of the fluoroquinolone drug class, gatifloxacin is also reported to be widely distributed with good penetration into many tissues. The major route of elimination of gatifloxacin is the kidney, resulting in diminished clearance in patients with renal impairment (1, 4).

Adverse effects

The severe effects of phototoxicity, QTc prolongation, hypoglycemia, and hepatotoxicity, which are associated with some of the fluoroquinolone antibiotics, have not been reported with gatifloxacin during clinical trials that evaluated patients for these effects. The most commonly reported adverse effects include nausea, diarrhea, headache, vaginitis, and dizziness. As with levofloxacin and ciprofloxacin, children and pregnant or lactating women should avoid using gatifloxacin due to articular damage that may occur with these agents (1, 5, 6).

Drug interactions

Drug interactions associated with the fluoroquinolone class are described in Table 1. Limited information is available on the potential for a pharmacodynamic interaction in humans between gatifloxacin and drugs that prolong the QTc interval of an electrocardiogram. The manufacturer recommends that gatifloxacin not be used concurrently in patients receiving class IA or class III antiarrhythmic agents (1).

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Table 1. Comparison of fluoroquinolone drug interactions*

Precipitant drug	Object drug	Effect	Description
Antacids Didanosine Iron salts Sucralfate Zinc salts	Fluoroquinolones	↓	Interferes with gastrointestinal absorption of the fluoroquinolones, resulting in decreased serum levels. Antacids should not be administered 2 to 4 hours before or after fluoroquinolone.
Probenecid	Fluoroquinolones	↑	Reduces ciprofloxacin renal clearance by 50%. Serum concentration is increased 50%.
Fluoroquinolones	Digoxin	↑	May slightly increase concentrations of digoxin; however, no dosage adjustment is recommended.
Fluoroquinolones	Anticoagulants	↑	May increase the effects of the anticoagulant. Coagulation studies should be monitored.
Fluoroquinolones	Cyclosporine	↑	May increase nephrotoxic effects. Renal functions should be closely monitored. Conflicting data exist.
Ciprofloxacin	Theophylline	↑	Decreases clearance and increases plasma levels, resulting in theophylline toxicity. This interaction is not expected to occur with gatifloxacin or levofloxacin; however, serum theophylline levels should be monitored if these agents are added to a drug regimen that already includes theophylline.

*Table material compiled from references 1, 2, 6-8.

Dosing and administration

The recommended dose of gatifloxacin is 400 mg, orally or by intravenous infusion, once every 24 hours, for all approved indications for patients whose calculated creatinine clearance is ≥ 40 mL/min. Dosage adjustment is necessary for patients with impaired renal function. For patients with a creatinine clearance < 40 mL/min or patients on hemodialysis or continuous peritoneal dialysis, the manufacturer recommends an initial dose of 400 mg with subsequent daily doses of 200 mg (1).

Clinical trials

Gatifloxacin has been evaluated in 15 efficacy trials, including 4 noncomparative and 11 double-blind, comparative trials, with a total enrollment of 6198 patients. Unfortunately, the published results of most of these studies are limited to abstracts or product information provided by the manufacturer.

The results of a clinical trial conducted in association with Bristol-Myers Squibb Company has been published in its entirety and compares gatifloxacin with levofloxacin for the treatment of community-acquired pneumonia (9). In the double-blind, prospective trial, 417 patients with clinically diagnosed community-acquired pneumonia were randomized to receive either 400 mg of oral or parenteral gatifloxacin or 500 mg of oral or intravenous levofloxacin therapy for 7 to 10 days. The most common infecting organisms were *Haemophilus parainfluenzae* (n = 30), followed by *Staphylococcus aureus*, *S. pneumoniae*, and *Mycoplasma pneumoniae*. In clinically evaluable patients, the response to therapy for the gatifloxacin group was 96% and for the levofloxacin group, 94%. Clinical response in microbiologically evaluable patients was 98% with gatifloxacin and 95% with levofloxacin. Gatifloxacin had a 98% bacteriologic eradication rate compared with a 93% rate with levofloxacin. All *H. influenzae*, *Moraxella catarrhalis*, *Klebsiella pneumoniae*, and *Legionella pneumoniae* isolates were eradicated or presumed eradicated in both groups. While it was reported that gatifloxacin-treated patients

had 100% (12 of 12) eradication of *S. pneumoniae* compared with 78% (14 of 18) of those treated with levofloxacin, this study lacks statistical power. Adverse events occurred with similar frequency in both treatment groups, with nausea, insomnia, and vaginitis being the most common.

An open-label, multicenter, noncomparative study was conducted to evaluate the safety and efficacy of 400 mg of oral gatifloxacin administered for 10 days to outpatients with acute, uncomplicated bacterial sinusitis (10). Of the 364 patients enrolled in the study, only 258 were clinically evaluable and 124 were microbiologically evaluable; 164 patients were excluded from the study because a pretreatment pathogen was not identified. The most common organisms isolated were *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*. Clinical success was defined as the resolution or improvement of the 3 cardinal signs and symptoms of acute infection (sinus pain, sinus tenderness, purulent discharge) without additional antimicrobial therapy. The clinical success rate was reported to be 95%. Of the clinically evaluable patients, 245 had resolution or improvement of facial pain, tenderness, and purulent discharge after 7 to 10 days of gatifloxacin therapy. Clinical success rate by pathogen was also evaluated, with a reported 96% bacteriologic eradication rate. Gatifloxacin had a 97% clinical efficacy against *S. pneumoniae* and a 100% efficacy against *H. influenzae* and *M. catarrhalis*. The most common adverse events associated with gatifloxacin were nausea, dizziness, diarrhea, headache, and vaginitis.

MOXIFLOXACIN

Moxifloxacin is a broad-spectrum fluoroquinolone antibiotic. It was approved by the FDA in December 1999 for the treatment of acute bacterial exacerbations of chronic bronchitis, acute bacterial sinusitis, and mild to moderate community-acquired pneumonia caused by susceptible strains of the microorganisms listed in Table 2 (11).

Table 2. Food and Drug Administration–approved indications for moxifloxacin*

Infection	Microorganism
Acute bacterial exacerbations of chronic bronchitis	<i>Haemophilus influenzae</i> <i>Haemophilus parainfluenzae</i> <i>Moraxella catarrhalis</i> <i>Klebsiella pneumoniae</i> <i>Streptococcus pneumoniae</i> <i>Staphylococcus aureus</i>
Acute bacterial sinusitis	<i>Haemophilus influenzae</i> <i>Moraxella catarrhalis</i> <i>Streptococcus pneumoniae</i>
Community-acquired pneumonia	<i>Streptococcus pneumoniae</i> <i>Haemophilus influenzae</i> <i>Mycoplasma pneumoniae</i> <i>Moraxella catarrhalis</i> <i>Chlamydia pneumoniae</i>

*Compiled from reference 8.

Pharmacology/pharmacokinetics

Similar to other fluoroquinolone agents, moxifloxacin exhibits bactericidal activity against susceptible bacteria through its inhibition of topoisomerases II (DNA gyrase) and IV. The structure of moxifloxacin contains a methoxy group at the 8 position and an azabicyclo moiety at the 7 position. Peak concentrations are seen 1 to 3 hours after moxifloxacin administration. The drug is metabolized by glucuronide and sulfate conjugation and is not affected by the cytochrome P450 enzyme systems. Approximately 45% of moxifloxacin is excreted as unchanged drug, with 20% in urine and 25% in feces. The pharmacokinetics of moxifloxacin are not altered in patients with mild, moderate, or severe renal insufficiency; therefore, dosage adjustments are not necessary in these populations. In patients with mild to moderate hepatic impairment, the peak moxifloxacin concentration was reduced 16%, and the area under the curve was reduced 23% compared with healthy controls. Dosage adjustments are not recommended for patients with mild hepatic insufficiency (Child Pugh class A); however, use is not recommended due to a lack of data in that patient population (11–13).

Adverse effects

The most common adverse events in clinical trials were nausea, diarrhea, headache, and dizziness. Most adverse events were mild to moderate and improved or resolved during follow-up. All fluoroquinolones have the potential to cause phototoxicity; however, this has not been observed with levofloxacin or in the limited clinical experience with moxifloxacin (12, 14–16).

Moxifloxacin prolongs the QTc interval in select patients. Its use should be avoided in patients with known prolongation of the QTc interval, patients with uncorrected hypokalemia, and patients receiving class IA (e.g., quinidine, procainamide) or class III (e.g., amiodarone, sotalol) antiarrhythmic agents. Moxifloxacin may produce an additive effect with other medications that prolong the QTc interval (e.g., cisapride, erythromycin, antipsychotics, and tricyclic antidepressants); therefore,

moxifloxacin should be administered with caution with these agents. Moxifloxacin should also be administered cautiously in patients with ongoing proarrhythmic conditions, clinically important bradycardia, or acute myocardial ischemia. The recommended dose of moxifloxacin should not be exceeded, as the magnitude of QTc prolongation may increase with increasing concentrations of the drug. QT-interval prolongation has not been reported with levofloxacin.

Moxifloxacin shares the quinolone-class warnings and precautions regarding use in pediatric populations, pregnant women, nursing women, and patients with central nervous system disorders. The class warnings regarding convulsions, increased intracranial pressure, psychosis, central nervous system stimulation, hypersensitivity reactions, pseudomembranous colitis, and tendon ruptures are similar as well (11).

Drug interactions

Interactions have not been observed when moxifloxacin has been administered concurrently with digoxin, glyburide, probenecid, ranitidine, theophylline, or warfarin (11).

Dosing and administration

The recommended dose of moxifloxacin is 400 mg given orally once a day. Therapy should continue for 5 to 10 days depending on the indication for its use (11).

Clinical trials

Acute exacerbation of chronic bronchitis. Moxifloxacin, 400 mg once daily for 5 days, was compared with clarithromycin, 500 mg twice daily for 7 days, in a double-blind study enrolling 750 patients with acute bacterial exacerbations of chronic bronchitis (14). Of these, 649 patients were evaluable. A total of 342 “causative” organisms were isolated: 49 isolates were resistant to clarithromycin, whereas none of the isolates had minimal inhibitory concentrations above the resistance breakpoint for moxifloxacin. The most common pathogens were *S. pneumoniae*, *H. influenzae*, *H. parainfluenzae*, *M. catarrhalis*, and *S. aureus*. Clinical success at day 14 was achieved in 89% of patients in the moxifloxacin group and 88% in the clarithromycin group. Follow-up at 21 to 28 days posttreatment showed a continued cure rate of 89% in both groups. Eradication rates were superior in the moxifloxacin group. However, the clinical outcome of clarithromycin was similar regardless of the susceptibility of isolates to clarithromycin. Adverse events were similar between the 2 groups and included nausea, diarrhea, dizziness, and headache. The lack of adequate statistical analysis in this trial makes it difficult to compare the efficacy of moxifloxacin and clarithromycin.

Acute sinusitis. Moxifloxacin, 400 mg once daily for 10 days, was compared with trovafloxacin, 200 mg once daily for 10 days, in a double-blind study enrolling 594 patients with symptoms and radiographic evidence of acute maxillary sinusitis (11). Clinical evaluation was available for 513 patients. Clinical success was reported in 88.1% of moxifloxacin-treated patients and 89.2% of trovafloxacin-treated patients at 7 to 14 days posttherapy. Adverse effects occurred more frequently in the trovafloxacin group (37% vs 33%), and more patients in the trovafloxacin group discontinued therapy due to adverse effects (7% vs 3%).

Dizziness was much more common in the trovafloxacin group (20% vs 5%, $P < 0.001$).

Moxifloxacin, 400 mg once daily for 10 days, was also compared with cefuroxime axetil, 250 mg twice daily for 10 days, in a double-blind trial enrolling 542 patients with acute bacterial sinusitis (11, 15). Clinical evaluation was available for 457 patients. Clinical success, defined as cure and improvement, was achieved in 89.7% of moxifloxacin-treated patients and 89.3% of cefuroxime-treated patients at 7 to 21 days posttherapy. Adverse effects considered to be drug-related were reported for 37% of moxifloxacin-treated patients and 26% of cefuroxime-treated patients. Nausea occurred most frequently with the moxifloxacin therapy (11% vs 4%) (12, 16).

Community-acquired pneumonia. In a study by Fogarty et al, moxifloxacin, 400 mg once daily for 10 days, was compared with clarithromycin, 500 mg twice daily for 10 days, in a double-blind trial enrolling 474 patients with clinically and radiologically documented community-acquired pneumonia (11, 16). At 14 to 35 days posttherapy, 382 patients were available for evaluation. The clinical success for this disease state was 95% in both treatment groups. Organisms were isolated prior to therapy in 56% of the evaluable patients. The most commonly isolated pathogens included *Chlamydia pneumoniae*, *M. pneumoniae*, *H. influenzae*, and *S. pneumoniae*. Bacteriologic eradication was achieved in 96% of patients in both treatment groups. Nausea and diarrhea were the most common side effects in both treatment groups, occurring in 8% to 9% of patients.

SUMMARY

As a third-generation fluoroquinolone, gatifloxacin would be expected to be at least comparable to levofloxacin in its ability to eradicate organisms currently susceptible to levofloxacin. While the chemical structure of gatifloxacin may offer an improved adverse effect profile over levofloxacin, this was not considered a significant finding in the clinical trials available for review. The pharmacokinetic profile of gatifloxacin appears to be similar to levofloxacin and provides the same advantage for once-daily dosing.

It is well known that among the fluoroquinolones, ciprofloxacin provides the best coverage against *Pseudomonas aeruginosa*. Gatifloxacin, levofloxacin, and ciprofloxacin appear to be uniformly active against other gram-negative organisms. Gatifloxacin appears to be similar to levofloxacin in its coverage of gram-positive and atypical pathogens and, therefore, may prove to be an alternative agent for the treatment of community-acquired pneumonia. At this time, resistance to levofloxacin is not a problem at our institution. Furthermore, it is difficult to thoroughly assess gatifloxacin's clinical efficacy based on the currently published clinical trials. The 2 trials included in this review consisted of small numbers of patients and lacked statistical power on which to base conclusions. In addition, gatifloxacin and levofloxacin share the same advantage of interchangeability be-

tween intravenous and oral administration as well as once-daily dosing.

Moxifloxacin has pneumococcal activity that is better than that of levofloxacin and similar to that of trovafloxacin. However, the absence of comparative trials between moxifloxacin and levofloxacin makes it difficult to assess the clinical significance of this enhanced activity against *S. pneumoniae*. Based on published clinical trials, it is also difficult to completely assess the clinical efficacy of moxifloxacin. There is concern about QT-interval prolongation with moxifloxacin, which does not occur with levofloxacin. Finally, the limited availability of moxifloxacin solely as an oral dosage form could potentially hamper the clinical utility of this drug.

It will be interesting to see how each of the new fluoroquinolone agents favors in a market where a suitable agent already exists. Postmarketing information will certainly play a role in defining the place in therapy for each of these new antimicrobial drugs.

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