

Safety and Tolerability of Fluoroquinolones

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Clinical trials in patients with community- and hospital-acquired infections have established that the clinical effectiveness and safety of fluoroquinolones are similar to β -lactam and macrolide agents. The most common drug-related adverse effects (AEs) with fluoroquinolone therapy involve the gastrointestinal tract and central nervous system and are usually transient and mild to moderate in severity. However, serious toxic reactions have led to the limited and restrictive use of trovafloxacin in the United States and the withdrawal of temafloxacin and grepafloxacin from worldwide markets. In addition, postmarketing spontaneous AE reports have imposed updates in the precautions and warning sections of product package inserts of selected fluoroquinolones. This article reviews the AEs associated with the fluoroquinolones and compares the safety profiles of ciprofloxacin, gatifloxacin, levofloxacin, and moxifloxacin. Clinical Cornerstone® Monograph. Copyright © 2004 Excerpta Medica, Inc.

ADVERSE EFFECTS ASSOCIATED WITH FLUOROQUINOLONES

Gastrointestinal Reactions

The most frequently reported adverse events (AEs) associated with the commonly used fluoroquinolones are gastrointestinal (GI) and central nervous system (CNS) reactions (1–3). These AEs are usually transient and mild to moderate in severity, and rarely require the discontinuation of therapy.

However, serious toxic reactions have led to the limited and restrictive use of trovafloxacin in the United States and the withdrawal of temafloxacin and grepafloxacin from worldwide markets (Table I) (4). In addition, postmarketing spontaneous AE reports have imposed updates in the precautions and warning sections of product package inserts (PIs) of selected fluoroquinolones.

The incidence of drug-related GI reactions ranges from 2% to 20% (1–3). The most frequently reported events are nausea, vomiting, and diarrhea. Other reported reactions are abdominal pain, anorexia, dyspepsia, and constipation (5–8). As with most other antibiotics, *Clostridium difficile*-associated diarrhea has been ascribed to fluoroquinolone use, but in a limited number of case reports and respective case-control studies.

Central Nervous System Reactions

CNS AEs are the second most frequently reported events and include headache, dizziness, and insomnia. The incidence of these drug-related CNS reactions ranges from 1% to 2%, and severity is usually mild to moderate (1–3). However, a number of

TABLE I. FLUOROQUINOLONES WITHDRAWN FROM THE MARKET OR PLACED ON RESTRICTIVE USE FOR SAFETY REASONS

<i>Fluoroquinolone</i>	<i>Safety Issues</i>	<i>Consequence</i>
Grepafloxacin	Cardiovascular events	Withdrawn 2 years after drug approval date
Temafloxacin	Hemolytic anemia, hypoglycemia in elderly patients, renal failure, abnormal liver test results, coagulopathy	Withdrawn ~4 months after drug approval date
Trovafloxacin	Hepatic failure	Restrictive use and black box warnings added to product insert 2 years after drug approval date

Adapted with permission (4).

other CNS AEs have been reported, such as restlessness, agitation, drowsiness, lightheadedness, tremors, and confusion. Delirium, acute psychosis, and convulsions also have been described in rare and selected instances (1,2,9). Most CNS effects occur early in therapy and usually resolve with discontinuation of the fluoroquinolone.

Dermatologic Reactions

The overall incidence of dermatologic AEs ranges from 0.5% to 3% (2). The most commonly reported reactions are mild and self-limiting skin rashes and pruritus. The intravenous administration of fluoroquinolones has been associated with injection site reactions and pain in 3.5% to 5% of patients. In contrast to other fluoroquinolones, gemifloxacin is associated with a drug-related rash that appears after a longer duration of therapy (eg, >7 days) and occurs more commonly in female patients <40 years or postmenopausal females taking hormone replacement therapy (10). Gemifloxacin-related rash is usually described as mild to moderate severity; however, up to 10% of patients have developed rash with severe intensity.

Photoallergic Reactions

Photoallergic reactions are rare and require prior exposure to a fluoroquinolone (11). Phototoxicity is generally considered uncommon (<0.1%) for ciprofloxacin, gatifloxacin, levofloxacin, and moxifloxacin (5–8). However, significant rates (1% to 16%) of phototoxic reactions have been associated with previously available (eg, lomefloxacin and

KEY POINT

GI reactions, eg, nausea, vomiting, and diarrhea, and CNS reactions, eg, headache, dizziness, and insomnia, are the most frequently reported AEs associated with the commonly used fluoroquinolones.

sparfloxacin) or investigational (eg, clinafloxacin and fleroxacin) agents (1–3). All of these agents have had a halogen such as a fluorine or chloride substituted in the X-8 position of the bicyclic ring (**Figure**) and as a result possess the highest potential for phototoxicity (12). Extensive exposure to ultraviolet light should generally be avoided during therapy with any fluoroquinolone. In addition, therapy should be discontinued if phototoxicity (eg, a skin eruption) occurs.

Anaphylactoid and Anaphylactic Reactions

Anaphylactoid and anaphylactic reactions have been reported during treatment of infections with fluoroquinolones. One report estimated the rate of anaphylactoid reactions with ciprofloxacin as 1.2 per 100,000 prescriptions (13). Because of their similar chemical structures, it may be advisable to avoid the use of any fluoroquinolone in a patient who has experienced an anaphylactic reaction.

Musculoskeletal Reactions

AEs associated with the musculoskeletal system and fluoroquinolones are either arthropathy or tendinopathy (2,3). Concern about fluoroquinolone-induced arthropathy derives from observational studies in juvenile animals. In humans, the incidence of fluoroquinolone-induced arthropathy is <1%, has typically involved the weight-bearing joints (2,3), and is more common in patients aged <30 years. The clinical presentation involves pain, stiffness, and synovial swelling. The onset of symptoms occurs during the first few days of treatment and usually resolves within a few days or weeks after discontinuation of fluoroquinolone therapy.

Fluoroquinolone-associated tendinopathy includes tendinitis and tendon rupture, with ~90 cases reported in the literature. The suggested incidence of fluoroquinolone-induced tendon injury in the healthy patient population is rare and is estimated to range from 0.14% to 0.4% (14). However, this incidence may be higher in patients with risk factors such as renal transplantation, renal failure,

hemodialysis, use of corticosteroids, age >50 years, and male athletes. Although the onset of symptoms usually occurs within 1 to 2 weeks after starting therapy, reports have described onset occurring as long as months after discontinuation of the fluoroquinolone. Most reports involve injuries to the Achilles tendon, and ruptures occur ~50% of the time. Recovery from the injury usually requires rest and immobilization for 1 to 2 months. Most reported cases have come from France in conjunction with a commonly used fluoroquinolone in that country, pefloxacin (not available in the United States). Although ciprofloxacin was the second most commonly reported agent involved in these tendon injuries, this AE is considered a class effect of all fluoroquinolones.

Renal and Hepatic Reactions

AEs involving the liver and kidneys are uncommon (15,16). The obvious exceptions have been with selected agents such as temafloxacin and trovafloxacin (2,17,18). In general, liver enzyme elevations occur in 2% to 3% of patients during

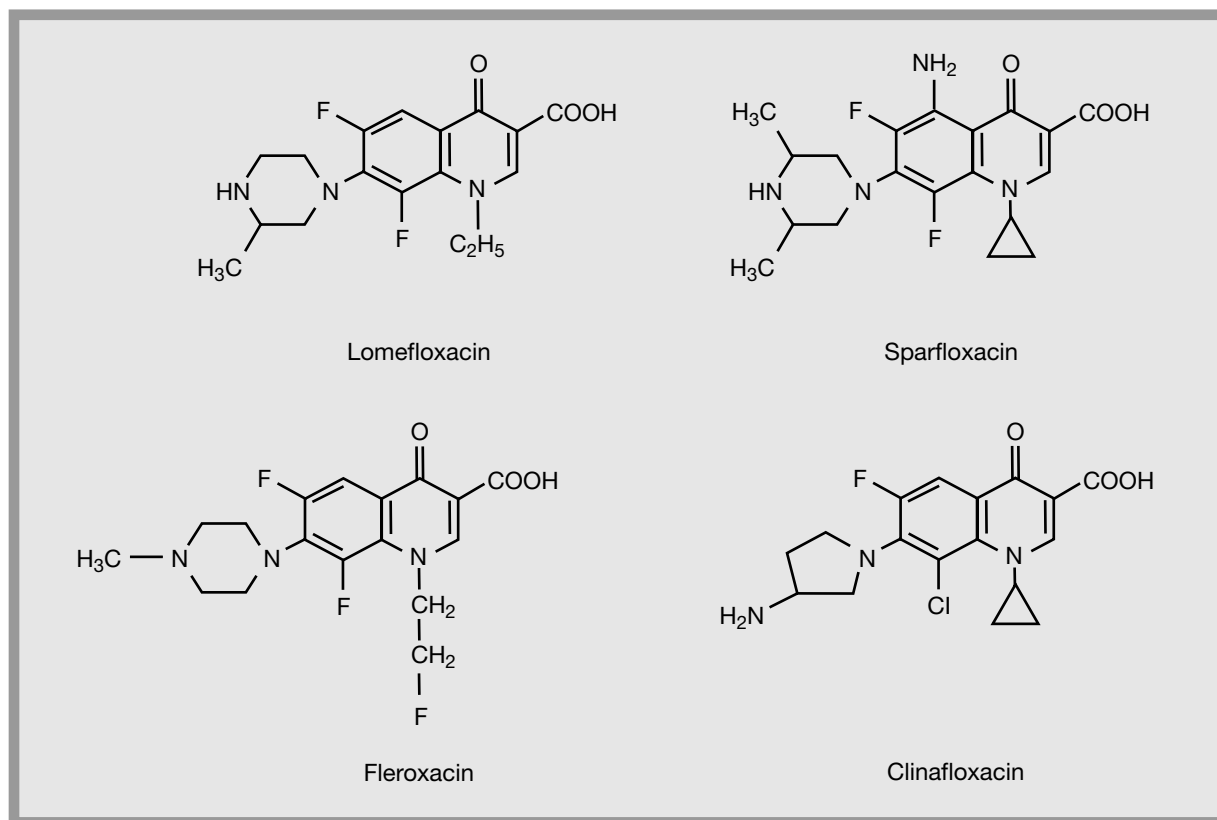


Figure. Chemical structures of fluoroquinolones associated with high rates of phototoxicity.

treatment with fluoroquinolones. The increases in transaminases and alkaline phosphatase are commonly in the magnitude of 2 to 3 times the upper limit of normal values, and these effects usually return to the normal range of laboratory values once the agent is discontinued. Limited cases of severe liver abnormalities have been reported, including cholestatic jaundice, hepatitis, liver necrosis, and hepatic insufficiency or failure (2,18). Incidences of reported renal injury include crystaluria, hematuria, interstitial nephritis, and acute renal failure (2,17).

KEY POINT

Careful monitoring of blood glucose is recommended for diabetic patients receiving fluoroquinolone therapy, especially gatifloxacin, which should be discontinued if a hypoglycemic reaction occurs.

Fluoroquinolones and Elderly and Diabetic Patients

The PIs for all fluoroquinolones outline the potential for disturbances of glucose homeostasis, including symptomatic hypoglycemia and hyperglycemia (5–8). Several of the agents no longer available (eg, enoxacin, lomefloxacin, temafloxacin) have been associated with hypoglycemia in elderly patients (2). In addition, concomitant administration of fluoroquinolones with glyburide has caused severe hypoglycemia (19,20). PIs generally have included class precautions, suggesting that these reactions usually occur in diabetic patients receiving concurrent treatment with insulin or an oral hypoglycemic agent (eg, glyburide or glibenclamide). Blood glucose should be carefully monitored in patients at risk of these reactions, and fluoroquinolone therapy should be discontinued and appropriate treatment started immediately if a hypoglycemic reaction occurs.

Recent postmarketing spontaneous AE reporting from several countries has indicated that hypoglycemia and hyperglycemia occur more fre-

quently with gatifloxacin than with other commonly used fluoroquinolones (7,21). Similar to previous reports, hypoglycemic reactions tended to occur in diabetic patients; however, many of the hyperglycemic episodes were observed in patients not previously diagnosed with diabetes. In addition, some of these reports include severe and sometimes life-threatening episodes of hyperosmolar nonketotic hyperglycemia coma. Consequently, these reports have initiated updated versions of the PI outlining the types of patients who may be at risk for these AEs (**Table II**) (7). The PI suggests that the incidence of hypoglycemic and hyperglycemic events in diabetic patients is 6.4 per 1000 and 13 per 1000 (21). In comparison, these respective events in nondiabetic patients occur in 0.3 per 1000 and 0.07 per 1000. Why gatifloxacin is associated with a higher frequency of disturbances to blood glucose is not known. It has been hypothesized that the blockade of adenosine triphosphate-sensitive potassium channels in pancreatic β -cells may result in a dose- or concentration-related increase or decrease in insulin release (22–24), which in part supports the observation that patients aged ≥ 65 years have an increased risk of severe hyperglycemia, secondarily due to age-related decreases in renal function and higher serum gatifloxacin concentrations (24). Caution may have to be exercised when prescribing gatifloxacin at the current recommended doses for elderly patients. Whether this AE can be avoided by using a lower dose of gatifloxacin (eg, 200 mg/d) needs further study.

Fluoroquinolones and Cardiac Dysrhythmias

Drug-associated cardiac dysrhythmias and the prolongation of electrographic QTc intervals (including torsades de pointes) remain issues of concern in the clinical use of fluoroquinolones (25,26).

Various animal and in vitro models have clearly demonstrated that fluoroquinolones are inhibitors of the human ether-a-go-go (*eag*)-related gene (HERG) potassium channel, and these agents can be associated with cardiac arrhythmias. Differences among these agents do exist in regard to the potency for potassium channel-blocking properties. Grepafloxacin and sparfloxacin are considered the

TABLE II. WARNING STATEMENTS REGARDING GATIFLOXACIN AND DISTURBANCES IN BLOOD GLUCOSE

<i>Adverse Event</i>	<i>Warning Statements</i>
Hypoglycemic episodes	<p>“Hypoglycemic episodes, in some cases severe, have been reported in patients with diabetes mellitus treated with either sulfonylurea or nonsulfonylurea oral hypoglycemic medications.”</p> <p>“These events frequently occurred on the first day of therapy and usually within 3 days following the initiation of gatifloxacin.”</p>
Hyperglycemic episodes	<p>“Hyperglycemic episodes, in some cases severe and associated with hyperosmolar nonketotic hyperglycemia coma, were reported in diabetic patients, most between 4 and 10 days following the initiation of gatifloxacin therapy. Many of these patients had other underlying medical problems and were receiving concomitant medications that may have contributed to the glucose abnormality.”</p> <p>“Episodes of hyperglycemia, including hyperosmolar nonketotic hyperglycemia coma, also occurred in patients not previously diagnosed with diabetes mellitus.”</p> <p>“Elderly patients who may have unrecognized diabetes, age-related decreased renal function, underlying medical problems, and/or are taking concomitant medications associated with hyperglycemia may be at particular risk for serious hyperglycemia.”</p>

Source: Tequin package insert (7).

most potent, whereas ciprofloxacin is a weak HERG potassium channel-inhibitor (25). The following rank order of potency has been suggested: sparfloxacin > grepafloxacin, moxifloxacin, gatifloxacin > levofloxacin, ciprofloxacin (23).

Cardiac-related fatalities and life-threatening ventricular arrhythmias have been associated with grepafloxacin and sparfloxacin (25). As a result, grepafloxacin has been withdrawn from the worldwide marketplace (4). All currently marketed fluoroquinolones have been associated with prolongation of the QTc interval in healthy subjects (5–8,25–30). PIs for the newer agents such as gatifloxacin and moxifloxacin have extensive warning labels regarding limited clinical experience with patients at high risk for QTc prolongation, electrolyte (eg, potassium) disorders, and concurrent treatment with drugs (eg, antipsychotics, tricyclic antidepressants, Class IA [eg, quinidine, procainamide] or Class III [eg, amiodarone, sotalol] antiarrhythmic agents) known to prolong the QTc interval (7,8). In addition, the recommended dose (400 mg once daily) or intravenous infusion rate of moxifloxacin should not be exceeded because the effects on prolongation of QTc interval are dose and/or concentration dependent (8,29,30). In contrast, no warnings appear in the ciprofloxacin PI, and

precaution statements indicate that rare cases of torsades de pointes occur in patients taking levofloxacin who have concurrent medical conditions or medications (5,6). Overall, cases of torsades de pointes have been rarely reported with the commonly used fluoroquinolones, especially in patients without risk factors for QTc interval prolongation (31).

KEY POINT

Although fluoroquinolones have demonstrated landmark safety profiles, their concentration-dependent AEs differ, which may limit the clinical use of high doses and long duration of therapy with some fluoroquinolones in some patients.

SAFETY OF HIGH FLUOROQUINOLONE DOSES

The bacteriologic and clinical responses of fluoroquinolones have been linked to ratios of maximum plasma concentration (C_{max}) to minimum inhibitory concentration (MIC) [C_{max}/MIC] and of 24-hour area under the concentration-time curve (AUC_{0-24}) to MIC [AUC_{0-24}/MIC] (32). These predictive pharmacody-

dynamic parameters suggest that high daily doses may have clinical benefit in serious and/or complicated infections, in preventing the emergence of bacterial resistance, and in shortening the duration of antibiotic therapy. The question is can high daily doses be safely administered with all fluoroquinolones?

Comparable rates of treatment-emergent, drug-related, and serious AEs have been demonstrated regardless of whether patients with community-acquired pneumonia (CAP) were treated with once-daily dosing regimens of either levofloxacin 500 mg or 750 mg for 10 and 5 days, respectively (32). For levofloxacin the once-daily dose of 750 mg for the treatment of complicated skin and skin-structure infections, the type, rate, and incidence of AEs have been demonstrated to be similar to the recommended once-daily dose of 250 mg for the treatment of urinary tract infections and to the once-daily 500-mg dose for uncomplicated skin and skin-structure infections, acute bacterial exacerbation of chronic bronchitis, CAP, and acute maxillary sinusitis (34). For the treatment of nosocomial pneumonia, a high rate of adverse and serious events was observed (1.8% to 8.6%) with the higher dosage of levofloxacin (750 mg once daily); however, this may have reflected severe underlying conditions of these patients as well as the use of other antimicrobials as part of the treatment regimen for this type of infection (35). Overall, the safety profile for levofloxacin has remained the same for dose ranges of 250 to 750 mg (6).

Clinical indications and the use of ciprofloxacin as approved by the US Food and Drug Administration have included a wide range of daily doses for mild, moderate, and severe infections caused by susceptible strains of pathogens (5). The oral and intravenous doses of ciprofloxacin for mild to moderate infections are 250 to 500 mg every 12 hours and 400 mg every 12 hours, respectively. These doses are increased to 750 mg orally every 12 hours and 400 mg intravenously every 8 hours for severe and/or complicated skin and skin-structure infections, bone and joint infections, and nosocomial pneumonia. The higher intravenous dose of ciprofloxacin 400 mg every 8 hours is based, in part, on the long-term safety data of oral ciprofloxacin, 750 mg every 12

hours, as well as similar systemic exposure parameters (C_{max} and AUC_{0-24}) associated with these 2 dosing regimens (36,37). Overall, the incidence and type of AEs have been similar within the dosage range of ciprofloxacin.

The currently approved dosage for gatifloxacin and moxifloxacin is 400 mg once daily. Limited information is available about the safety of these 2 agents at higher doses. Because concentration-dependent AEs have been associated with hyperglycemia and the use of fluoroquinolones, it is unlikely that the gatifloxacin dosage should be escalated, especially in patients at high risk of these AEs (24). Similarly, the recommended dose of 400 mg of moxifloxacin probably should not be exceeded because significant and further prolongation of the QTc interval has been observed with doses of 800 mg and 1200 mg (25–30).

SUMMARY

Over the past 15 years, fluoroquinolones have demonstrated landmark safety profiles. Ciprofloxacin and levofloxacin remain 2 of the safest and best-tolerated fluoroquinolones over a wide range of daily doses. Gatifloxacin and moxifloxacin are promising agents; however, little post-marketing safety data are available compared with ciprofloxacin and levofloxacin. In addition, concentration-dependent AEs (eg, disturbances in blood glucose and prolongation of the QTc interval) may limit the clinical use of high doses and long duration of therapy with some fluoroquinolones in some patients.

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