

Clinical Safety Profile of Fluoroquinolones



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Fluoroquinolones are considered safe and well-tolerated anti-infective agents that are commonly used to treat community-acquired and healthcare-associated infections. The most frequent reported adverse events (e.g. gastrointestinal and central nervous system [CNS] reactions) are usually transient and mild to moderate in severity. However, serious adverse reactions have led to the withdrawal of temafloxacin and grepafloxacin from worldwide markets, and restrictive and limited use of trovafloxacin in the United States. Rare and agent-specific adverse events have included alterations in glucose homeostasis (e.g. gatifloxacin), prolongation of QTc interval (e.g. moxifloxacin), and skin rash (e.g. gemifloxacin). High-dose therapy for serious infections or short-course therapy has been limited to ciprofloxacin and levofloxacin secondary to their excellent tolerability and lower rates of adverse events compared to other, currently available, fluoroquinolones.

Introduction

Fluoroquinolones have demonstrated comparable efficacy and rates of adverse events as β -lactam and/or macrolide agents in the treatment of community-acquired and healthcare-associated infections. Fluoroquinolones currently marketed are generally considered to have good safety profiles (1–5). However, post-marketing spontaneous adverse event reports have imposed updates in the precautions and warning sections of product package inserts of fluoroquinolones. In addition, higher rates of serious toxic reactions has resulted in restricted or suspended use of trovafloxacin, worldwide withdrawal of temafloxacin and grepafloxacin, and discontinued development of fleroxacin, BAY 3118, and clinafloxacin (4–8) (Table 1). The purpose of this paper is to review the adverse events associated with fluoroquinolone therapy, with an emphasis on safety profiles of ciprofloxacin, levofloxacin, gatifloxacin, moxifloxacin, and gemifloxacin.

Relationships between molecular structure and adverse reactions

Potential adverse reactions have been associated with specific chemical modifications of the basic molecular structure of fluoroquinolones (9) (Figure 1). Phototoxicity and central nervous sys-

tem (CNS) adverse events tend to be associated with modifications at positions 1, 5, 7, and 8. A greater incidence of phototoxic reactions appears when the substitution at position C-8 is a halogen, such as fluorine (lomefloxacin, sparfloxacin, fleroxacin) or chlorine (clinafloxacin, sitafloxacin) (Figure 2). Recent studies suggest that fluoroquinolone phototoxicity is also influenced by the substituent at position 1 (10).

Alterations of the molecular structure at position 7 seem to have the greatest influence on CNS effects (9). Unsubstituted piperazinyl and pyrrolidinyl moieties exhibit higher binding affinity to the gamma-aminobutyric acid (GABA) receptor site. A reduction in GABA-mediated inhibitory transmission may increase the excitability of the CNS.

Fluoroquinolones that have a 2, 4-difluorophenyl moiety at position C-1 (Figure 3) have been associated with unexpected and severe idiosyncratic drug reactions (e.g. hepatitis [trovafloxacin], hemolytic-uremic syndrome [temafloxacin], eosinophilic pneumonitis [tosufloxacin]) (3,4,7,8). No definitive study has confirmed a cause-effect relationship is associated with the similar C-1 molecular modifications of temafloxacin, trovafloxacin, and tosufloxacin.

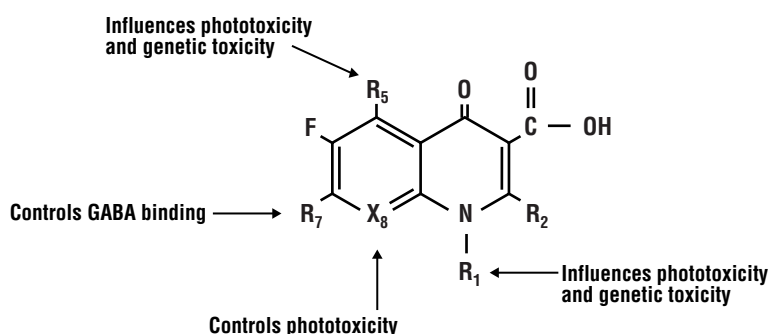
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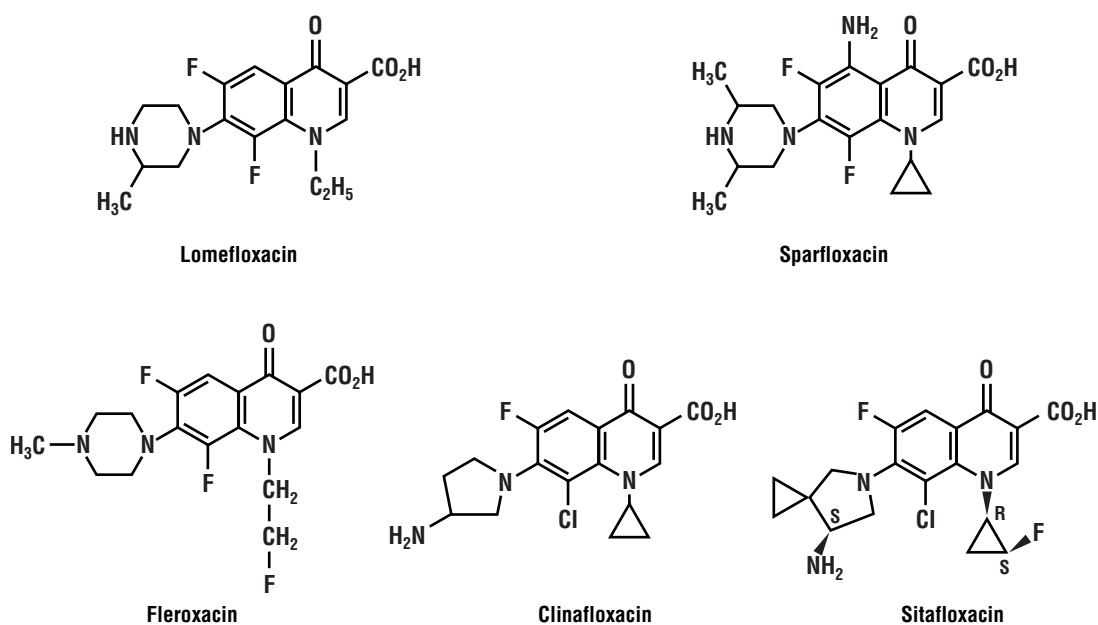
Table 1. Selected landmarks in fluoroquinolones safety

Date	Fluoroquinolone	Adverse event	Implications
June 1992	Temafloxacin	Hemolytic anemia, hypoglycemia, renal failure, abnormal liver function tests, coagulopathy	Withdrawn from worldwide market
March 1993	Lomefloxacin	Phototoxicity	Product package insert warnings added
Mid-1990s	Various agents	Tendinitis, tendon rupture	Class language added to product package insert
December 1996	Sparfloxacin	Phototoxicity, QTc prolongation	Product package insert warnings added
June 1999	Trovafloxacin	Hepatic toxicity	Public health advisory on use issued
October 1999	Grepafloxacin	Cardiovascular events	Withdrawn from worldwide market
November 1999	Clinafloxacin	Phototoxicity, CNS reactions	Clinical development discontinued
December 1999	Moxifloxacin, Gatifloxacin	QTc prolongation	Product package insert warnings added
Mid-2002	Gatifloxacin	Glucose homeostasis	Product package insert warnings added

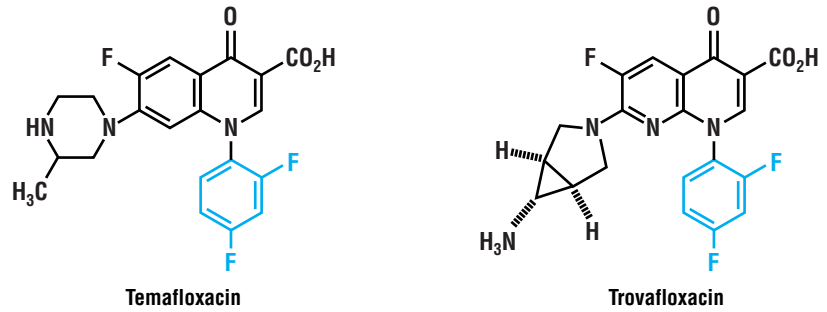
Abbreviation: CNS = central nervous system.

Figure 1. Adverse events associated with the molecular structure of fluoroquinolones.

Abbreviation: GABA = gamma-aminobutyric acid.
Adapted from reference (9).

Figure 2. Molecular structure of fluoroquinolones associated with higher rates of phototoxicity.

Adapted from reference (9).

Figure 3. Molecular structure of temafloxacin and trovafloxacin.

Adapted from reference (9).

Adverse effects of fluoroquinolones

Ciprofloxacin, levofloxacin, gatifloxacin, moxifloxacin, and gemifloxacin are currently the most commonly marketed fluoroquinolones. These agents are well tolerated and appear to be free of severe immunologically mediated adverse drug reactions. The most common drug-related adverse events are gastrointestinal (GI), CNS, and dermatologic reactions. These adverse events are usually considered mild to moderate in severity and rarely result in a discontinuation of fluoroquinolone therapy (1–5) (Table 2). Rare adverse events have been reported (e.g. torsades de points, glucose homeostasis abnormalities, severe skin reactions), but are more likely associated with specific agents and patient populations.

GI reactions

The most common drug-related adverse events caused by fluoroquinolone therapy involve the GI tract (1–5) (Table 2). The incidence of drug-related GI events among currently used fluoroquinolones is 2–20% (1–3). The most frequently reported reactions are nausea, vomiting, and diarrhea; while abdominal pain, anorexia, dyspepsia, and constipation have also been reported (11–15). Fluoroquinolone-associated GI effects tend to be

mild in severity and rarely require the discontinuation of therapy. The fluoroquinolones most likely to cause adverse GI events (floxacin, grepafloxacin, trovafloxacin, sparfloxacin) are not available for clinical use. Grepafloxacin, for example, caused dose-related GI adverse reactions, including a high incidence of metallic taste (9–18%) and vomiting (up to 10%) (16,17).

CNS reactions

Reactions involving the CNS are the second most frequently reported adverse events during fluoroquinolone therapy. Headache, dizziness, and insomnia are the most commonly reported events (1–5). The incidence of these drug-related CNS reactions ranges from 1% to 2%, and severity is usually mild to moderate. However, a wide range of other CNS adverse effects have been reported including restlessness, agitation, drowsiness, light-headedness, tremors, and confusion. Delirium, acute psychosis, and convulsions have been described in rare and selected instances (1–3,18). Most CNS effects occur early in therapy and usually resolve with discontinuation of the drug.

There is a higher probability of CNS adverse events among fluoroquinolones that are no longer used (e.g. BAY 3118, floxacin, trovafloxacin,

Table 2. Comparative adverse events and discontinuation rates (%) for selected fluoroquinolones

	Ciprofloxacin	Levofloxacin	Gatifloxacin	Moxifloxacin	Gemifloxacin
Gastrointestinal effects					
Nausea	5.0	1.0	3.0–6.0	7.2	2.7
Vomiting	2.0	0.2	2.0	1.0–2.0	0.9
Diarrhea	2.0	1.0	3.0–6.0	5.7–8.0	3.6
Abdominal pain	2.0	0.3	< 3.0	2.0	0.9
CNS effects					
Dizziness	1.0–2.0	0.3	1.0–2.0	3.0	0.8
Headache	1.0	0.1	≥ 0.1–< 3.0	2.0–8.0	1.2
Dermatologic effects	< 1.0	0.3	≥ 0.1–< 3.0	≥ 0.1–< 2.0	2.8
Discontinuation rate	1.2–3.5	1.3–3.7	3.0–5.0	2.0–5.0	2.2

Abbreviation: CNS = central nervous system.

Adapted from reference (2,11–15).

grepafloxacin, sparfloxacin) (5,18–20). For example, trovafloxacin caused dose-related CNS adverse events such as dizziness in 3% of patients receiving a 100 mg dose and 11% of patients receiving a 200 mg dose (21). In addition, the incidence, intensity, and duration of dizziness and lightheadedness increased at doses higher than 300 mg, and occurred more frequently in young female patients (22).

Dermatologic reactions

The incidence of dermatologic adverse effects resulting from fluoroquinolone therapy ranges from 0.5% to 3% (1–5). Most of these skin reactions are reported as mild, self-limiting skin rashes and pruritis.

The overall rate of skin rash for gemifloxacin has been reported as 2.8%, which is approximately two to three times higher than comparator agents, including other fluoroquinolones (15). The severity of this drug-related rash has usually been described as mild to moderate, however up to 10% of patient have experienced a rash of severe intensity. The rash usually resolves in 60–80% of patients within 7–14 days after discontinuation of gemifloxacin therapy.

Rash has been described as an uncomplicated exanthematous (morbilliform) skin reaction, and has not been associated with eosinophilia or severe or toxic manifestations (e.g. Stevens-Johnson Syndrome, mucous erythema multiforme, toxic epidermal necrolysis). The rash most commonly occurs after 8–10 days of therapy, in female patients younger than 40 years of age, and postmenopausal women receiving hormone replacement therapy

(Figure 4). Prolonged therapy (> 7 days) should be avoided and gemifloxacin should be discontinued in patients who develop a rash.

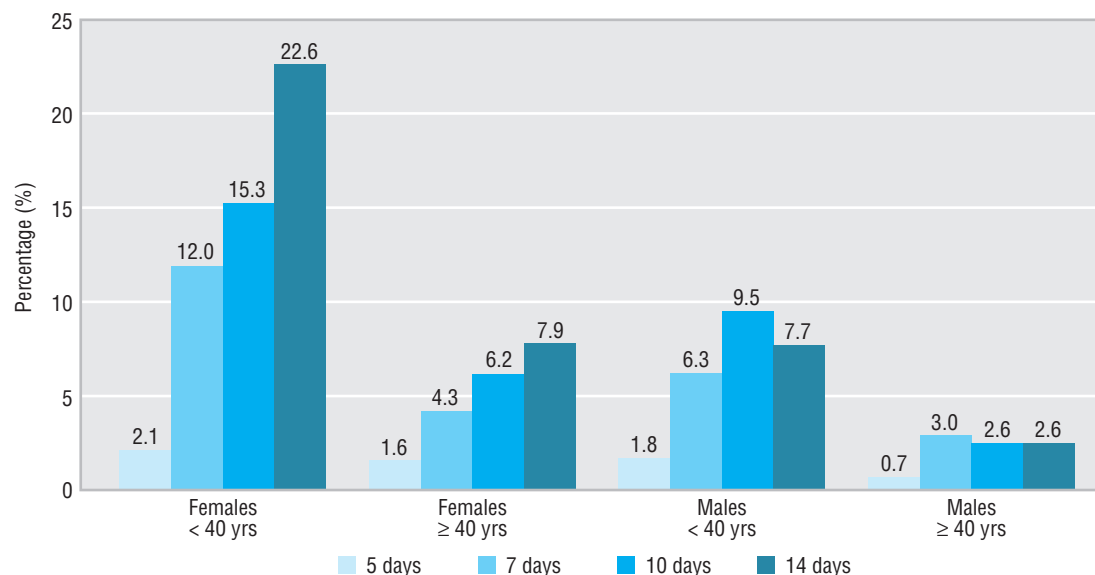
Photosensitivity is an uncommon, but distinctive adverse reaction specific to individual fluoroquinolones. Two types of photosensitivity have been described: photoallergy and phototoxicity. Photoallergic reactions are rare and require prior exposure to a fluoroquinolone; it is thought to be a manifestation of cell-mediated immunity (23). Phototoxicity is generally considered uncommon (< 0.1%) for ciprofloxacin, levofloxacin, gatifloxacin, moxifloxacin, and gemifloxacin (11–15). However, significant rates (1–16%) of phototoxic reactions have been associated with previously available (lomefloxacin, sparfloxacin) or investigational (floxacin and clinafloxacin) agents (1–5). As previously discussed, all of these agents have had a halogen such a fluorine or chloride substituted in the X-8 position of the agent's bicyclic ring (9) (Figure 2). It is recommended that extensive exposure to ultraviolet light should generally be avoided during therapy with any fluoroquinolone, and that therapy should be discontinued if phototoxicity (e.g. a skin eruption) occurs.

The intravenous administration of fluoroquinolone has been associated with injection site reactions and pain in 3.5–5% of patients. The recommended intravenous infusion period for injectable fluoroquinolones is 60 minutes, while the infusion period should be extended to 90 minutes for the 750 mg dose of levofloxacin (12).

Anaphylactoid and anaphylactic reactions

Anaphylactoid and anaphylactic reactions have

Figure 4. Incidence of gemifloxacin-associated skin rash categorized by sex, age, and duration of therapy.



Adapted from reference (15).

been reported to occur with all fluoroquinolones (24). The estimated rate of anaphylactoid reactions for ciprofloxacin is 1.2 per 100,000 prescriptions (25). A quinolone-specific immunoglobulin E (IgE) has been associated with the various forms of type I reactions (e.g. urticaria, angioedema, and anaphylactic shock) (26). Desensitizations have been shown to be successfully administered (27,28). However, the use of fluoroquinolones should be avoided in any patient who has previously experienced an immediate hypersensitivity reaction because of significant cross-reactivity and similar chemical structures among the various agents.

Musculoskeletal reactions

Adverse events associated with the musculoskeletal system are either arthropathy or tendinopathy (1–4). In humans, the incidence of fluoroquinolone-induced arthropathy is less than 1%. It has typically involved the weight bearing joints and is more common in patients < 30 years of age (2,3). The clinical presentation includes 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 drug therapy.

Concern about fluoroquinolone-induced arthropathy is a result of observation studies restricted to juvenile animals, except for pefloxacin where data exists for both skeletally mature and immature dogs (4,29). A comprehensive review of the published literature concluded that observed fluoroquinolone-induced arthropathy in animals does not correlate with the use of these agents in children and adolescents (30). Reports on the use of ciprofloxacin, norfloxacin, ofloxacin, and nalidixic acid in more than 7,000 skeletally immature patients have not demonstrated the development of arthralgia beyond what might be expected as a result of an underlying disease. In addition, several recent reports involving gatifloxacin provide further evidence of the safety profile in pediatric patients (31–33). The United States Food and Drug Administration (FDA) has recently approved ciprofloxacin for the treatment of infections in children (11). Despite the increasing evidence on the safety of fluoroquinolones for treating pediatric patients, the appropriate use and increasing selective pressure that favors drug-resistant microorganisms remains controversial.

Fluoroquinolone-associated tendinopathy has included tendinitis and tendon rupture, with approximately 90 cases reported in the literature (34). The suggested incidence of fluoroquinolone-induced tendon injury in the healthy patient population is rare (approximately 0.14–0.4%). However,

this incidence may be higher in patients with select risk factors such as renal transplantation, renal failure, hemodialysis, use of corticosteroids, age > 50, and male athletes (34,35). Although the onset of symptoms usually occurs within 1–2 weeks after starting therapy, reports have described onset as long as months after discontinuation of the fluoroquinolone. The majority of reports involve injuries to the Achilles tendon and ruptures occur in approximately 50% of these cases. Recovery from the injury usually requires rest and immobilization for 1–2 months. The most frequent reports have come from France and are attributed to perfloxacin, which is commonly used in that country (it is unavailable in the US). Although ciprofloxacin was the second most commonly reported antimicrobial associated with these tendon injuries, they are considered a class effect for all fluoroquinolones.

Renal and hepatic reactions

Adverse events to the liver and kidneys are uncommon reactions with fluoroquinolones (36,37). In general, liver enzyme elevations occur in 2–3% of patients during treatment with fluoroquinolones. The increases in transaminases and alkaline phosphatase are usually two to three times the upper limit of normal levels. These ranges generally return to normal laboratory values once the agent is discontinued. There are limited case reports of severe liver abnormalities including cholestatic jaundice, hepatitis, liver necrosis, and hepatic insufficiency or failure (2,8). For renal injury, there are reports of crystalluria, hematuria, interstitial nephritis, and acute renal failure (2,7).

The obvious exceptions with fluoroquinolone-associated renal and/or hepatic reactions have been temafloxacin and trovafloxacin (2,7,8). Temafloxacin was withdrawn shortly after its initial market approval because of “temafloxacin syndrome”, which consisted of hemolytic anemia, renal failure, abnormal liver functions test, hypoglycemia and/or coagulopathy (7). In comparison, trovafloxacin was placed on restrictive use in the United States and removed from the market in Europe within two years after its approval. Trovafloxacin therapy resulted in more than 100 reported cases of clinically symptomatic and severe liver toxicity. The public health advisory issued by the FDA stated that 14 cases of acute liver failure had been reported, with five deaths due to liver-related illnesses and four patients requiring liver transplantation (one of whom subsequently died) (8). The mechanisms of these higher incidence and severity of renal and hepatic adverse reactions remains unknown.

Glucose homeostasis reactions

The incidence of glucose homeostasis reactions (e.g. hypoglycemia and hyperglycemia) among currently available fluoroquinolones is considered extremely low (< 2%) (38). The product package insert outlines the potential for symptomatic hypoglycemia and/or hyperglycemia reactions (11–15). In general, the product information has included class precautions and suggests that these reactions usually occur in diabetic patients receiving concurrent treatment with insulin or an oral hypoglycemic agent (e.g. glyburide or glibenclamide). It is recommended that careful monitoring of blood glucose is needed in patients at risk of these reactions. Fluoroquinolone therapy should be discontinued and appropriate treatment started immediately if a hypoglycemic reaction occurs.

It does appear that some fluoroquinolones are more commonly associated with higher rates of serious glucose homeostasis reactions in susceptible patient populations. Historically, lomefloxacin, enoxacin, and temafloxacin were associated with hypoglycemia in elderly patients (2). The incidence of hypoglycemia events during Phase II and III clinical trials was much higher in patients treated with clinafloxacin (4%) versus comparator agents (1.1%) (4). In addition, clinafloxacin was associated with significant decreases in blood glucose levels in healthy subjects secondary to extensive increases in insulin concentrations (39). More recently, retrospective studies, case reports, and post-marketing surveillance have indicated that hypoglycemia and hyperglycemia occur more often with gatifloxacin than with other commonly used antimicrobial agents, including fluoroquinolones (13,38,40–45).

lones (13,38,40–45).

Frothingham has recently obtained and reviewed the FDA spontaneous adverse event reports for ciprofloxacin, levofloxacin, gatifloxacin, and moxifloxacin during the period November 1997 to September 2003 (45). Gatifloxacin accounted for 80% (453, $n = 568$) of all adverse event reports for glucose homeostasis abnormalities and 68% (17, $n = 25$) of reported fatalities. In addition, glucose homeostasis reactions accounted for 24% of all reported adverse event reports for gatifloxacin, significantly higher ciprofloxacin (1.3%), levofloxacin (1.6%), and moxifloxacin (1.3%). The exact reasons why gatifloxacin is associated with a higher frequency of disturbances to blood glucose are not known. It has been hypothesized that blockade of ATP-sensitive potassium channels in pancreatic beta cells may result in a dose- or concentration-related increase or decrease in insulin release (46–49). *In vitro* studies support the clinical findings that temafloxacin and gatifloxacin have a much greater likelihood of inducing these changes compared to levofloxacin or moxifloxacin.

Several safety-related changes have occurred in the labeling of the FDA-approved product package insert for gatifloxacin (13) (Table 3). Similar to previous reports, the hypoglycemic reactions tend to occur in diabetic patients, while hyperglycemic episodes occurred in patients not previously diagnosed with diabetes. Caution should be exercised when prescribing gatifloxacin in patients with diabetes mellitus or in elderly patients. The latter recommendation is supported, in part, by the observations that elderly patients (≥ 65 years) are at an increased risk of severe hyperglycemia second-

Table 3. Warning statements regarding gatifloxacin and disturbances in blood glucose

Adverse event	Warning statements
Hypoglycemic episodes	<p>“Hypoglycemic episodes, in some cases severe, have been reported in patients with diabetes mellitus treated with either sulfonylurea or non-sulfonylurea 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 non-ketotic hyperglycemic coma, were reported in diabetic patients, mostly 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 non-ketotic hyperglycemic coma, also occurred in patients not previously diagnosed with diabetes mellitus.”</p> <p>“Elderly patients who may have unrecognized diabetes, age-related decrease renal function, underlying medical problems, and/or are taking concomitant medications associated with hyperglycemia may be at particular risk for serious hyperglycemia.”</p>

Adapted from reference (13).

arily due to age-related decreases in renal function and higher serum gatifloxacin concentrations (50). Further studies are needed to determine whether hyperglycemia can be avoided by using a lower dose of gatifloxacin (200 mg/day).

Cardiovascular reactions

The prolongation of electrographic QTc intervals and its potential complications have emerged as safety issues for fluoroquinolones (51,52). Historically, cardiac-related fatalities and life-threatening ventricular arrhythmias have been associated with sparfloxacin and grepafloxacin. In part, these adverse events led to the withdrawal of grepafloxacin from the worldwide market and contributed towards sparfloxacin's withdrawal from the US market (2–4).

Numerous *in vitro* and animal models have clearly demonstrated that fluoroquinolones are inhibitors of the human ether a-go-go-related gene (HERG) potassium channel and these agents can be associated with cardiac arrhythmias (53–55). All fluoroquinolones produce a dose-dependent prolongation of the QTc interval and differences in the potency for potassium channel blocking properties among these agents exist. Almost all studies conclude that sparfloxacin and grepafloxacin are the most potent HERG potassium channel inhibitors, while ciprofloxacin is one of the weakest (51). The potency of fluoroquinolones has been ranked and, in general, typical findings suggest the following order: sparfloxacin > grepafloxacin \geq moxifloxacin = gatifloxacin \gg levofloxacin, ciprofloxacin (22).

A limited number of studies have evaluated effects of the currently available fluoroquinolones on the prolongation of the QTc interval in healthy subjects (56–58). A double-blind, randomized, placebo-controlled, crossover study comparing single doses of levofloxacin demonstrated that the mean QTc values after drug administration were not significantly different from placebo at the 500 mg and 1000 mg dose levels (56). Mean QTc interval prolongation was significantly greater for levofloxacin 1500 mg compared to the placebo.

In a second comparative study involving single oral doses of ciprofloxacin 1500 mg, levofloxacin 1000 mg, moxifloxacin 800 mg (each of these doses were twice the FDA-recommended dose at that time), the mean changes in QTc intervals at several end points were significantly greater for moxifloxacin than those with placebo, ciprofloxacin or levofloxacin (57). The effect of single 400 mg and 800 mg oral doses of moxifloxacin has also been evaluated in healthy subjects (58). The increase in QT interval duration compared to placebo ranged from 2.3% to 4.5% across the

entire RR intervals evaluated. A significant correlation between the percent change of QT interval and moxifloxacin plasma concentrations was observed ($r = 0.72, p < 0.001$). Finally, moxifloxacin has more recently been used as a positive control in several comparative trials evaluating prolongation of the QTc intervals with various therapeutic agents (59, 60).

Only a few cases of drug-associated cardiac dysrhythmias (including torsades de pointes) have been reported among the currently marketed fluoroquinolones (52,61–64). However, the product package inserts of gatifloxacin, moxifloxacin, and gemifloxacin have extensive warnings about the limited clinical experiences of these agents in patients at high risk of QTc prolongation, electrolyte (potassium) disorders, and concurrent treatment with drugs (antipsychotics, tricyclic antidepressants, Class IA [e.g., quinidine, procainamide] or Class III [e.g., amiodarone, sotalol] antiarrhythmic agents) known to prolong the QTc interval (13–15). In addition, the recommended dose (400 mg once daily) or intravenous infusion rate (60 minutes) of moxifloxacin should not be exceeded since the effects on prolongation of QTc interval are dose- and/or concentration-dependent (14,58).

In contrast, no warnings appear in the ciprofloxacin package insert, while precaution statements for levofloxacin indicate that rare cases of torsades de pointes may occur in patients with concurrent medical conditions or medications (11,12). Overall, cases of torsades de pointes have rarely been reported among currently used fluoroquinolones, especially in patients without risk factors for QTc interval prolongation. The multiple risk factors for QTc interval prolongation and torsades de pointes must be carefully evaluated before prescribing fluoroquinolones in susceptible patient populations.

Safety of high-dose fluoroquinolone therapy

Ciprofloxacin and levofloxacin have established safety profiles in a broad range of clinical indications and daily doses. The FDA-approved clinical indications for ciprofloxacin include mild, moderate, and severe infections caused by susceptible strains of pathogens (11). The oral and intravenous doses of ciprofloxacin for mild to moderate infections are 250–500 mg every 12 hours and 400 mg every 12 hours, respectively. An oral dose of ciprofloxacin 750 mg every 12 hours and 400 mg intravenously every 8 hours is recommended 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 was based

on, in part, the long-term safety data of oral ciprofloxacin 750 mg every 12 hours, as well as similar systemic exposure parameters (maximum plasma concentration [C_{max}] and area under the curve [AUC_{0-24}]) associated with these two dosing regimens (65,66). Overall, the incidence and type of adverse events have been similar across all dose ranges of ciprofloxacin.

The recommended daily doses of levofloxacin have included 250 mg for the treatment of urinary tract infections and 500 mg for uncomplicated skin and skin structure infections, acute exacerbations of chronic bronchitis (AECB), community-acquired pneumonia (CAP), acute maxillary sinusitis, and chronic bacterial prostatitis (12). The initial indications for a higher dose (750 mg once daily) of levofloxacin included more serious infections such as nosocomial pneumonia and complicated skin and skin structure infections (67,68). Comparable rates of treatment-emergent, drug-related, and serious adverse effects have been demonstrated regardless which once-daily dosing regimen (250 mg, 500 mg or 750 mg) of levofloxacin is used (12). For the treatment of nosocomial pneumonia, a slightly higher rate of adverse and serious events were observed with the 750 mg once-daily dose of levofloxacin, however this might be more reflective of the severe underlying conditions and concomitant antimicrobial therapy in patients with this type of infection (67). Overall, the safety profile for levofloxacin has remained the same for dose ranges of 250 to 750 mg (12).

One of the most recent trends in antimicrobial therapy is the use of higher doses with shorter duration of therapy. The World Health Organization has encouraged drug development programs to focus on optimizing treatment regimens with regards to safety, efficacy, and the prevention of selecting resistant microorganisms (69). One of the considerations has been shorter courses of antimicrobial therapy in an attempt to reduce the disruption of the normal flora, decrease the selective pressure that favors drug-resistant microorganisms, and encourage patient adherence.

In multicenter, noninferiority studies involving adults with either CAP or acute bacterial sinusitis, a short course of 750 mg of levofloxa-

cin once daily for 5 days was well tolerated and as effective as the traditional 10-day course of levofloxacin 500 mg (70,71). No significant differences in drug-related adverse events were demonstrated when these two dosages were compared in a combined analysis of these clinical studies (72). Similar safety profile has been demonstrated for short courses (3 or 5 days) of levofloxacin 750 mg for the treatment of AECB (73).

The potential role and safety profile of gatifloxacin and moxifloxacin at higher daily doses (greater than 400 mg once daily) is not clear (13,14). Since concentration-dependent adverse effects have been associated with these fluoroquinolones, it is unlikely that the dose of gatifloxacin should be escalated, especially in elderly or diabetic patients who are at higher risk for hypoglycemia or hyperglycemia (50). Similarly, the recommended dose of moxifloxacin 400 mg should probably not be exceeded since significant and further prolongation of the QTc interval has been observed with doses of 800 mg and 1200 mg.

The recommended dose and treatment durations of gemifloxacin include 320 mg once daily for 5–7 days of therapy (15). The duration, and probably the dose, of gemifloxacin should not be increased because of the higher incidence of drug-related rash.

Summary

Fluoroquinolones have demonstrated important landmark safety profiles during the past two decades. Ciprofloxacin and levofloxacin are well-tolerated with established safety profiles in a broad range of clinical indications and daily doses. In general, gatifloxacin, moxifloxacin, and gemifloxacin are well-tolerated agents at the currently recommended doses and durations of therapy. However, each of these fluoroquinolones has also been linked to rare adverse effects (e.g. disturbances in blood glucose, prolongation of the QTc interval, and skin rashes) in susceptible patient populations. It seems prudent to avoid higher doses and longer durations of therapy until further safety information is available for gatifloxacin, moxifloxacin, and gemifloxacin.

REFERENCES

- 1 Lipsky BA, Baker CA. Fluoroquinolone toxicity profiles: a review focusing on newer agents. *Clin Infect Dis* 1999; 28: 352–64.
- 2 Fish DN. Fluoroquinolone adverse effects and drug interactions. *Pharmacotherapy* 2001; 21 (10 Pt 2): 253S–272S.
- 3 Rodvold KA. Clinical safety profile of newer fluoroquinolones. *J Crit Illness* 1999; 14 (Suppl): S28-40.
- 4 Owens RC Jr, Ambrose PG. Antimicrobial safety: focus on fluoroquinolones. *Clin Infect Dis* 2005; 41 (Suppl 2): S144–57.
- 5 Rubinstein E. History of quinolones and their side effects. *Chemother* 2001; 47 (Suppl 3): 3–8.
- 6 Lasser KE, Allen PD, Woolhandler SJ, Himmelstein DU, Wolfe SM, Bor DH. Timing of new black box warnings and withdrawals for prescription medications. *JAMA* 2002; 287: 2215–20.
- 7 Blum MD, Graham DJ, McCloskey CA. Terafloxacin syndrome: review of 95 cases. *Clin Infect Dis* 1994; 18: 946–50.
- 8 Lumpkin MM. Public Health Advisory, Food and Drug Administration: Trovan (trovafloxacin/alatrofloxacin) [Letter]. June 9, 1999.
- 9 Domagala JM. Structure-activity and structure-side-effect relationships for the quinolone antibacterials. *J Antimicrob Chemother* 1994; 33: 685–706. Erratum in: *J Antimicrob Chemother* 1994; 34: 851.
- 10 Hayashi N, Nakata Y, Yazaki A. New findings on the structure-phototoxicity relationship and photostability of fluoroquinolones with various substituents at position 1. *Antimicrob Agents Chemother* 2004; 48: 799–803.
- 11 Cipro (ciprofloxacin) [package insert]. West Haven, CT: Bayer Pharmaceuticals Corporation, April 2005.
- 12 Levaquin (levofloxacin) [package insert]. Raritan, NJ: Ortho-McNeil Pharmaceutical Inc., August 2005.
- 13 Tequin (gatifloxacin) [package insert]. Princeton, NJ: Bristol-Myers Squibb Company, May 2005.
- 14 Avelox (moxifloxacin hydrochloride) [package insert]. West Haven, CT: Bayer Pharmaceuticals Corporation, July 2005.
- 15 Factive (gemifloxacin) [package insert]. Waltham, MA: Oscient Pharmaceuticals, August 2004.
- 16 Langan CE, Zuck P, Vogel F, McIvor A, Peirzchala W, Smakal M, et al. Randomized, double-blind study of short-course (5 day) grepafloxacin versus 10 day clarithromycin in patients with acute bacterial exacerbations of chronic bronchitis. *J Antimicrob Chemother* 1999; 44: 515–23.
- 17 Chodosh S, Lakshminarayan S, Swarz H, Breisch S. Efficacy and safety of a 10-day course of 400 or 600 milligrams of grepafloxacin once daily for treatment of acute bacterial exacerbations of chronic bronchitis: comparison with a 10-day course of 500 milligrams of ciprofloxacin twice daily. *Antimicrob Agents Chemother* 1998; 42: 114–20.
- 18 Bowie WR, Willetts V, Jewesson PJ. Adverse reactions in a dose-ranging study with a new long-acting fluoroquinolone, fleroxacin. *Antimicrob Agents Chemother* 1989; 33: 1778–82.
- 19 Bowie WR, Willetts V, Megran DW. Dose-ranging study of fleroxacin for treatment of uncomplicated *Chlamydia trachomatis* genital infections. *Antimicrob Agents Chemother* 1989; 33: 1774–7.
- 20 Schmuck G, Schurmann A, Schluter G. Determination of the excitatory potencies of fluoroquinolones in the central nervous system by an *in vitro* model. *Antimicrob Agents Chemother* 1998; 42: 1831–6. Erratum in: *Antimicrob Agents Chemother* 1998; 42: 2465.
- 21 Trovan (trovafloxacin) [package insert]. New York, New York: Pfizer, December 1997.
- 22 Teng R, Harris SC, Nix DE, Schentag JJ, Foulds G, Liston TE. Pharmacokinetics and safety of trovafloxacin (CP-99,219), a new quinolone antibiotic, following administration of single oral doses to healthy male volunteers. *J Antimicrob Chemother* 1995; 36: 385–94.
- 23 Gould JW, Mercurio MG, Elmets CA. Cutaneous photosensitivity diseases induced by exogenous agents. *J Am Acad Dermatol* 1995; 33: 551–73.
- 24 Campi P, Pichler WJ. Quinolone hypersensitivity. *Curr Opin Allergy Clin Immunol* 2003; 3: 275–81.
- 25 Davis H, McGoodwin E, Reed TG. Anaphylactoid reactions reported after treatment with ciprofloxacin. *Ann Intern Med* 1989; 111: 1041–3.
- 26 Manfredi M, Severino M, Testi S, Macchia D, Ermini G, Pichler WJ, et al. Detection of specific IgE to quinolones. *J Allergy Clin Immunol* 2004; 113: 155–60.
- 27 Gea-Banacloche JC, Metcalfe DD. Ciprofloxacin desensitization. *J Allergy Clin Immunol* 1996; 97: 1426–7.
- 28 Lantner RR. Ciprofloxacin desensitization in a patient with cystic fibrosis. *J Allergy Clin Immunol* 1995; 96: 1001–2.
- 29 Burkhardt JE, Hill MA, Lamar CH, Smith GN Jr, Carlton WW. Effects of difloxacin on the metabolism of glycosaminoglycans and collagen in organ cultures of articular cartilage. *Fundam Appl Toxicol* 1993; 20: 257–63.
- 30 Burkhardt JE, Walterspiel JN, Schaad UB. Quinolone arthropathy in animals versus children. *Clin Infect Dis* 1997; 25: 1196–204.
- 31 Pichichero ME, Arguedas A, Dagan R, Sher L, Saez-Llorens X, Hamed K, et al. Safety and efficacy of gatifloxacin therapy for children with recurrent acute otitis media (AOM) and/or AOM treatment failure. *Clin Infect Dis* 2005; 41: 470–8.
- 32 Brook I. Gatifloxacin therapy in otitis media in children. *Curr Infect Dis Rep* 2005; 7: 163–4.
- 33 Dagan R, Arguedas A, Schaad UB. Potential role of fluoroquinolone therapy in childhood otitis media. *Pediatr Infect Dis J* 2004; 23: 390–8.
- 34 Khaliq Y, Zhanell GG. Fluoroquinolone-associated tendinopathy: a critical review of the literature. *Clin Infect Dis* 2003; 36: 1404–10.
- 35 van der Linden PD, Sturkenboom MC, Herings RM, Leufkens HM, Rowlands S, Stricker BH. Increased risk of achilles tendon rupture with quinolone antibacterial use, especially in elderly patients taking oral corticosteroids. *Arch Intern Med* 2003; 163: 1801–7.
- 36 Clark DW, Layton D, Wilton LV, Pearce GL, Shakir SA. Profiles of hepatic and dysrhythmic cardiovascular events following use of fluoroquinolone antimicrobials: experience from large cohorts from the Drug Safety Research Unit Prescription-Event Monitoring database. *Drug Saf* 2001; 24: 1143–54.
- 37 Lomaestro BM. Fluoroquinolone-induced renal failure. *Drug Saf* 2000; 22: 479–85.
- 38 Owens RC Jr. Fluoroquinolone-associated dysglycemia: a tale of two toxicities. *Pharmacotherapy* 2005; 25: 1291–5.
- 39 Shailer PA, Randinitis E, Rausch G, et al. Effect of clinafloxacin on serum insulin and glucose levels in healthy subjects [abstract]. *Clin Pharmacol Ther* 1997; 61: 148.
- 40 Menzies DJ, Dorsainvil PA, Cunha BA, Johnson DH. Severe and persistent hypoglycemia due to gatifloxacin interaction with oral hypoglycemic agents. *Am J Med* 2002; 113: 232–4.
- 41 Health Products and Food Branch, Marketed Health Products Directorate. Gatifloxacin (Tequin): hypoglycemia and hyperglycemia. Canadian Adverse Reaction Newsletter 2003; 13(3): 1–2.
- 42 Hypoglycemia and hyperglycemia with fluoroquinolones. *Med Lett Drugs Ther* 2003; 45: 64.

- 43** Graumlich JF, Habis S, Avelino RR, Salverson SM, Gaddamanugu M, Jamma K, et al. Hypoglycemia in inpatients after gatifloxacin or levofloxacin therapy: nested case-control study. *Pharmacotherapy* 2005; 25: 1296–302.
- 44** Mohr JF, McKinnon PS, Peymann PJ, Kenton I, Septimus E, Okhuysen PC. A retrospective, comparative evaluation of dysglycemias in hospitalized patients receiving gatifloxacin, levofloxacin, ciprofloxacin, or ceftriaxone. *Pharmacotherapy* 2005; 25: 1303–9.
- 45** Frothingham R. Glucose homeostasis abnormalities associated with use of gatifloxacin. *Clin Infect Dis* 2005; 41: 1269–76.
- 46** Maeda N, Tamagawa T, Niki I, Miura H, Ozawa K, Watanabe G, et al. Increase in insulin release from rat pancreatic islets by quinolone antibiotics. *Br J Pharmacol* 1996; 117: 372–6.
- 47** Zunkler BJ, Was M. Effects of lomefloxacin and norfloxacin on pancreatic β -cell ATP-sensitive K^{+} channels. *Life Sci* 2003; 73: 429–35.
- 48** Saraya A, Yokokura M, Gono T, Seino S. Effects of fluoroquinolones on insulin secretion and β -cell ATP-sensitive K^{+} channels. *Eur J Pharmacol* 2004; 497: 111–7.
- 49** Gavin JR 3rd, Kubin R, Choudhri S, Kubitza D, Himmel H, Gross R, et al. Moxifloxacin and glucose homeostasis: a pooled-analysis of the evidence from clinical and postmarketing studies. *Drug Saf* 2004; 27: 671–86.
- 50** Ambrose PG, Bhavnani SM, Cirincione BB, Piedmonte M, Grasela TH. Gatifloxacin and the elderly: pharmacokinetic-pharmacodynamic rationale for a potential age-related dose reduction. *J Antimicrob Chemother* 2003; 52: 435–40.
- 51** Owens RC Jr. Risk assessment for antimicrobial agent-induced QTc interval prolongation and torsades de pointes. *Pharmacotherapy* 2001; 21: 301–19.
- 52** Owens RC Jr, Ambrose PG. Torsades de pointes associated with fluoroquinolones. *Pharmacotherapy* 2002; 22: 663–72.
- 53** Kang J, Wang L, Chen XL, Triggler DJ, Rampe D. Interactions of a series of fluoroquinolone antibacterial drugs with the human cardiac K^{+} channel HERG. *Mol Pharmacol* 2001; 59: 122–6.
- 54** Anderson ME, Mazur A, Yang T, Roden DM. Potassium current antagonist properties and proarrhythmic consequences of quinolone antibiotics. *J Pharmacol Exp Ther* 2001; 296: 806–10.
- 55** Patmore L, Fraser S, Mair D, Templeton A. Effects of sparfloxacin, grepafloxacin, moxifloxacin, and ciprofloxacin on cardiac action potential duration. *Eur J Pharmacol* 2000; 406: 449–52.
- 56** Noel GJ, Goodman DB, Chien S, Solanki B, Padmanabhan M, Natarajan J. Measuring the effects of supratherapeutic doses of levofloxacin on healthy volunteers using four methods of QT correction and periodic and continuous ECG recordings. *J Clin Pharmacol* 2004; 44: 464–73.
- 57** Noel GJ, Natarajan J, Chien S, Hunt TL, Goodman DB, Abels R. Effects of three fluoroquinolones on QT interval in healthy adults after single doses. *Clin Pharmacol Ther* 2003; 73: 292–303.
- 58** Demalis JL, Kubitza D, Tenneze L, Funck-Brentano C. Effect of single oral dose of moxifloxacin (400 mg and 800 mg) on ventricular repolarization in healthy subjects. *Clin Pharmacol Ther* 2000; 68: 658–66.
- 59** Barriere S, Genter F, Spencer E, Kitt M, Hoelscher D, Morganroth J. Effects of a new antibacterial, telavancin, on cardiac repolarization (QTc interval duration) in healthy subjects. *J Clin Pharmacol* 2004; 44: 689–95.
- 60** Morganroth J, Ilson B, Shaddinger BC, Dabiri GA, Patel BR, Boyle DA, et al. Evaluation of vardenafil and sildenafil on cardiac repolarization. *Am J Cardiol* 2004; 93: 1378–83, A6.
- 61** Bertino JS Jr, Owens RC Jr, Carnes TD, Iannini PB. Gatifloxacin-associated corrected QT interval prolongation, torsades de pointes, and ventricular fibrillation in patients with known risk factors. *Clin Infect Dis* 2002; 34: 861–3.
- 62** Amankwa K, Krishnan SC, Tisdale JE. Torsades de pointes associated with fluoroquinolones: importance of concomitant risk factors. *Clin Pharmacol Ther* 2004; 75: 242–7.
- 63** Samaha FF. QTc interval prolongation and polymorphic ventricular tachycardia in association with levofloxacin. *Am J Med* 1999; 107: 528–9.
- 64** Frothingham R. Rates of torsades de pointes associated with ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, and moxifloxacin. *Pharmacotherapy* 2001; 21: 1468–72.
- 65** Echols RM. The selection of appropriate dosages for intravenous ciprofloxacin. *J Antimicrob Chemother* 1993; 31: 783–7.
- 66** Pryka R, Kowalsky S, Haverstock D. Efficacy and tolerability of twice-daily ciprofloxacin 750 mg in the treatment of patients with acute exacerbations of chronic bronchitis and pneumonia. *Clin Ther* 1998; 20: 141–55.
- 67** West M, Boulanger BR, Fogarty C, Tennenberg A, Wiesinger B, Oross M, et al. Levofloxacin compared with imipenem/cilastatin followed by ciprofloxacin in adult patients with nosocomial pneumonia: a multicenter, prospective, randomized, open-label study. *Clin Ther* 2003; 25: 485–506.
- 68** Graham DR, Talan DA, Nichols RL, Lucasti C, Corrado M, Morgan N, et al. Once-daily, high-dose levofloxacin versus ticarcillin-clavulanate alone or followed by amoxicillin-clavulanate for complicated skin and skin-structure infections: a randomized, open-label trial. *Clin Infect Dis* 2002; 35: 381–9.
- 69** World Health Organization. WHO Global Strategy for Containment of Antimicrobial Resistance [online]. Available from: URL: http://www.who.int/csr/resources/publications/drugresist/HO_CDS_CSR_DRS_2001_2/EN/en.
- 70** Dunbar LM, Wunderink RG, Habib MP, Smith LG, Tennenberg AM, Khashab MM, et al. High-dose, short-course levofloxacin for community-acquired pneumonia: a new treatment paradigm. *Clin Infect Dis* 2003; 37: 752–60. Erratum in *Clin Infect Dis* 2003; 37: 1147.
- 71** Poole MD, Portugal PG, Xiang JX, Oross M, Tennenberg A, Kahn J. Efficacy of levofloxacin 750 mg for 5-days in the treatment of acute maxillary sinusitis: a randomized, double-blind study. Poster presented at: American Academy of Allergy, Asthma and Immunology's 61st Meeting; March 18–22, 2005; San Antonio, Texas.
- 72** Ambruzs M, Xiang JX, Fisher A, Khashab M, Kahn J. The safety of high-dose (750 mg qd) levofloxacin. Poster presented at: 43rd Annual Meeting of the Infectious Diseases Society of America; October 6–9, 2005; San Francisco, California.
- 73** Martinez FJ, Grossman RF, Zadeiki N, Fisher AC, Walker K, Ambruzs ME, et al. Patient stratification in the management of acute bacterial exacerbation of chronic bronchitis: the role of levofloxacin 750 mg. *Eur Respir J* 2005; 25: 1001–10.