Safety Concerns with Fluoroquinolones

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OBJECTIVE: To review the chemistry, pharmacology, and safety of fluoroquinolones.

DATA SOURCES: A MEDLINE search (1966–July 2007) was conducted using the key words fluoroquinolones or quinolones with safety, adverse effects, hypoglycemia, hyperglycemia, dysglycemia, QTc prolongation, torsades, seizures, phototoxicity, tendon rupture, *Clostridium difficile*, and pseudomembranous colitis for articles published in the English language.

STUDY SELECTION AND DATA EXTRACTION: Medicinal chemistry, in vitro, animal, and human trials were reviewed for information on the chemistry, pharmacology, and safety of each fluoroquinolone. Clinical trials were reviewed and included to compare the safety of systemic fluoroquinolones on the market. Literature on the pathology of serious adverse effects was also reviewed.

DATA SYNTHESIS: Gatifloxacin has been shown to increase the risk of hospitalization for dysglycemia in patients with and without diabetes. Hyperglycemia may occur with any fluoroquinolone, especially if not properly dose adjusted. Hypoglycemia may occur with any fluoroquinolone and has a higher frequency in patients receiving concomitant oral hypoglycemic drugs or insulin. Use of any fluoroquinolone should be avoided in patients with risk factors for QTc interval prolongation or tendinopathy. All fluoroquinolones should be used with caution in patients with a history of seizure disorders and may cause phototoxicity or *C. difficile*-associated diarrhea (CDAD).

CONCLUSIONS: Clinicians should be aware of possible alterations in blood glucose, QTc interval prolongation, seizures, phototoxicity, tendinopathy, or CDAD with the use of any fluoroquinolone, especially in patients with other risk factors for these conditions. Clinicians should closely monitor for these adverse effects and appropriately adjust doses to minimize these risks. To provide safe treatment for patients needing antibiotic therapy, an assessment of the risk–benefit ratio may be warranted in the decision to use a fluoroquinolone.

KEY WORDS: adverse effects, fluoroquinolones, safety.

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Fluoroquinolones are frequently used for the treatment of a variety of infectious diseases. This drug class is popular because of its relatively broad spectrum of activity, multiple approved indications for use, and high bioavailability, resulting in comparable blood concentrations when given intravenously or orally. The manufacturer of gatifloxacin, one agent in this class, removed it from the market after several cases of dysglycemia were determined to be associated with its use. No other manufacturer of a fluoroquinolone has taken a similar action. To determine whether there are any differences in safety associated with agents in this class, we review the chemistry and pharmacology of the fluoroquinolones and focus on adverse effects associated with the use of representative agents.

Chemistry and Structure

The quinolone nucleus consists of a bicyclic ring structure. There are fluoroquinolone structure–activity relationships and structure–adverse effect relationships based on constituents found at specific sites on the quinolone nucleus.[1] All drugs in the class possess a carboxyl group at position 3, a keto group at position 4, a fluorine atom at position 6, and either a piperazinyl group or a methylpiperazinyl group at position 7.[2] Position 1 influences a drug's potency, pharmacokinetics, and potential for interaction with theophylline. Positions 2, 3, and 4 are involved in binding to bacterial enzymes and are key to antibacterial activity. No adverse effects have been associated with position 2; positions 3 and 4 are responsible for the chelation of metals and thus the potential for all agents in the class to interact with divalent cations.

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Position 5 controls activity against gram-positive microorganisms and a fluoroquinolone's potential for phototoxicity. A methoxy group at position 5 is not only associated with greater gram-positive antimicrobial activity, but also with greater phototoxicity. The addition of a fluorine atom at position 6 (hence the name *fluoroquinolone*) enhances inhibitory activity against DNA gyrase and facilitates a drug's entry into the bacterial cell. All of the fluoroquinolones contain a fluorine atom at this position, and this constituent has not been associated with adverse effects.

Like position 1, position 7 influences an agent's potency, pharmacokinetics, and potential for interaction with theophylline. Structural differences at position 7 also influence a drug's spectrum of activity, with a piperazine moiety at this position providing increased antipseudomonal activity and a pyrrolidine group providing increased activity against gram-positive microorganisms. Position 7 also influences binding activity to γ-aminobutyric acid (GABA) in the brain and thus accounts for differences in central nervous system adverse effects among agents in the class.

A second fluorine atom added at position 8 increases absorption and half-life but is also a strong predictor of phototoxicity. The addition of a methoxy group at position 8 increases activity against *Streptococcus pneumoniae* and affinity for target bacterial enzymes, thus decreasing an agent's susceptibility to microbial resistance. The addition of a halogen atom at position 8 increases the activity of a compound against anaerobic microorganisms. However, it has also been determined that dihalogenated fluoroquinolones (compounds containing a fluorine atom at position 6 and another halogen at any other position) have a higher degree of phototoxicity.[1,3-5]

Safety

The most common adverse reactions associated with fluoroquinolone use in clinical trials were nausea and diarrhea.[6-9] In clinical trials with gemifloxacin, rash was found in 2.8% of patients.[6] More serious, but less commonly encountered, adverse effects include alterations in blood glucose levels, QTc interval prolongation, seizures, phototoxicity, tendinopathy, and *Clostridium difficile*–associated diarrhea (CDAD).

We reviewed the literature in an attempt to determine whether there are any differences in safety among drugs in the fluoroquinolone class.

Alteration of Glucose Levels

Recent findings suggest that glucose alterations may occur with fluoroquinolones at a higher incidence than what was initially believed. However, there are several risk factors for hypoglycemia and hyperglycemia that must be taken into account during evaluation of the causality of a medication, including a fluoroquinolone, as the true etiology of glucose disturbance. Risk factors for hypoglycemia include advanced age, increased serum creatinine, decreased albumin, liver disease, chronic heart failure, malignancy, sepsis, female sex, and concomitant treatment with a sulfonylurea or insulin.[10-12] Risk factors for hyperglycemia include decreased insulin secretion or decreased insulin sensitivity, as found in type 1 and type 2 diabetes mellitus, respectively; advanced age; high carbohydrate intake; infection; stress; and use of corticosteroids.[13] These confounders must be taken into account when evaluating a drug's risk for causing dysglycemia. Some studies did not show an increased risk of dysglycemia with gatifloxacin[14,15]; however, several case reports and other publications reported associations between the use of gatifloxacin and dysglycemia.[16-23] In February 2006, the manufacturer of gatifloxacin, Bristol-Myers Squibb, added a contraindication for its use in diabetic patients, and on May 4, 2006, announced that it was withdrawing the drug from the market.[24,25]

Although clinical development of clinafloxacin, a compound with a chlorine atom at position 8, was halted because it was associated with high incidence of hypoglycemia and phototoxicity, researchers have not yet identified an obvious structural moiety that increases a drug's risk of causing dysglycemia. The mechanism of fluoroquinolone-induced hypoglycemia is believed to be inhibition of adenosine triphosphate–sensitive potassium (K_{ATP}) channels in β-cells of the pancreas. These channels are key components in the regulation of insulin secretion. When K_{ATP} channels are inhibited, the membranes of β-cells become depolarized, ultimately resulting in the release of insulin. Saraya et al.[26] studied the effects of levofloxacin, gatifloxacin, and temafloxacin (which was never marketed) on the K_{ATP} channels of pancreatic β-cells in mice. They found that, although levofloxacin had little effect on K_{ATP} channels and insulin secretion, both gatifloxacin and temafloxacin directly inhibited these channels, thus significantly increasing insulin secretion. Insulin secretion increased in a dose-dependent manner as the concentration of gatifloxacin or temafloxacin was increased. This study suggests that levofloxacin does not affect insulin secretion, while gatifloxacin and temafloxacin cause insulin secretion through direct inhibition of pancreatic β-cell potassium channel activity.

Two nested case–control studies were conducted to identify differences in incidences of inpatient hospitalization for hypoglycemia and hyperglycemia after outpatient treatment with an oral macrolide (azithromycin, clarithromycin, or erythromycin), a second-generation cephalosporin (cefuroxime axetil or cefaclor), or a fluoroquinolone (gatifloxacin, levofloxacin, moxifloxacin, or ciprofloxacin) within one month prior to hospitalization.[23] Patients hospitalized for treatment of hypoglycemia were more likely to have been treated with gatifloxacin than with a macrolide (adjusted OR 4.3; 95% CI 2.9 to 6.3). Levofloxacin was

also associated with an increased incidence of hypoglycemia compared with a macrolide (adjusted OR 1.5; 95% CI 1.2 to 2). Patients hospitalized for treatment of hyperglycemia were also more likely to have been treated with gatifloxacin compared with a macrolide (adjusted OR 16.7; 95% CI 10.4 to 26.8). No other antibiotics were associated with dysglycemia. The authors concluded that outpatient use of gatifloxacin increased the risk of hospitalization for hypoglycemia and hyperglycemia in patients with and without diabetes. It is interesting that this study was published less than 2 months before the manufacturer announced that it was removing gatifloxacin from the market.[25]

A retrospective chart review of 17,108 hospitalized patients was conducted to evaluate the rates of dysglycemia with gatifloxacin, ciprofloxacin, levofloxacin, and ceftriaxone.[13] Dysglycemia was defined as a serum blood glucose concentration greater than 200 mg/dL or below 50 mg/dL that occurred within 72 hours after a dose of one of these antimicrobials was administered. Of the 1376 patients who had an abnormal blood glucose concentration, 93% had not received gatifloxacin, ciprofloxacin, levofloxacin, or ceftriaxone and were not included in the data analysis. Of patients who experienced dysglycemia, 91% had hyperglycemia and 9% developed hypoglycemia. Rates of dysglycemia were 1.01% with gatifloxacin, 0% with ciprofloxacin, 0.93% with levofloxacin, and 0.18% with ceftriaxone. Dysglycemia was significantly more likely to occur in patients receiving either levofloxacin or gatifloxacin compared with ceftriaxone (RR 3.32; 95% CI 2.31 to 4.78; $p < 0.05$). There was no significant difference in the rate of dysglycemia between gatifloxacin and levofloxacin (RR 1.07; 95% CI 0.62 to 1.86; $p = 0.8$). Concomitant sulfonylurea therapy was the only independent risk factor identified for hypoglycemia in patients who received fluoroquinolones. This study showed a higher risk of dysglycemia with levofloxacin versus ceftriaxone and highlights the importance of monitoring for hypoglycemia, especially in patients receiving sulfonylureas.

Graumlich et al.[27] compared the incidence of hypoglycemia between gatifloxacin and levofloxacin in a nested case–control study of 7287 hospitalized patients. Case patients included those who experienced a hypoglycemic event, defined as a blood glucose level less than 51 mg/dL plus a symptom consistent with hypoglycemia, within 96 hours of a dose of gatifloxacin or levofloxacin. Using logistic regression analysis, the authors determined that renal failure, sepsis, and any hypoglycemic drug therapy were significantly associated with hypoglycemia. After controlling for these independent risk factors, the risk of hypoglycemia was significantly higher with gatifloxacin versus levofloxacin (OR 2.81; 95% CI 1.02 to 7.70; $p = 0.045$). This study suggests an association between hypoglycemia and exposure to gatifloxacin and a higher risk compared with levofloxacin.

Based on the results of the previously cited studies, ciprofloxacin and levofloxacin do not appear to be independently associated with dysglycemia. However, there have been case reports of hypoglycemia occurring in patients who received ciprofloxacin plus glyburide[28,29] and of hypoglycemia associated with levofloxacin use in both diabetic and nondiabetic patients.[30-32] A pooled analysis of Phase 2 and 3 clinical trials and postmarketing surveillance studies found no clinically relevant effects of moxifloxacin on blood glucose levels.[33] Although no studies using gemifloxacin have been performed, data shown in its prescribing information show an incidence of possible or probable drug-related hyperglycemia in 0.1–1% of patients and no cases of hypoglycemia.[6] Clinicians should be aware of the rare but possible occurrence of hypoglycemia with the use of any fluoroquinolone and should vigilantly monitor blood glucose in patients receiving concomitant treatment with a sulfonylurea or insulin.

Although the mechanism of fluoroquinolone-induced hypoglycemia has been described, the mechanism of the more commonly occurring hyperglycemia is not known. One study that evaluated 10 patients who developed hyperglycemia while on gatifloxacin showed an association between hyperglycemia and lack of dose adjustment in patients with renal insufficiency.[34] This suggests an association between supratherapeutic concentrations of fluoroquinolones and hyperglycemia.

QTc Interval Prolongation

Prolongation of the QTc interval has been associated with fluoroquinolone use and can lead to torsade de pointes (TdP), a potentially life-threatening ventricular arrhythmia.[35] QTc interval prolongation is defined as a QTc interval greater than 450 msec in males and greater than 470 msec in females, although the arrhythmia generally occurs with a QTc interval of greater than 500 msec.[36] The acquired form of QTc interval prolongation is most commonly drug induced and led to the removal of the fluoroquinolones sparfloxacin and grepafloxacin from the market.[36,37] Although it is often difficult to establish causality of TdP, especially in patients receiving drugs that increase the risk for this arrhythmia, risk factors include female sex, hypokalemia, bradycardia, heart failure, treatment with digoxin or its derivatives, QTc interval prolongation at baseline, severe hypomagnesemia, and concomitant use of class Ia (eg, quinidine, procainamide) or class III antiarrhythmic drugs (eg, sotalol, amiodarone).[35]

Although it has been hypothesized that structural differences at position 5 of the quinolone nucleus affect cardiotoxicity, researchers have not yet identified an obvious structural moiety that increases an agent's risk for QTc prolongation.[36,38] The mechanism of fluoroquinolone-induced QTc prolongation is complex and is related to blockade of

the rapid acting portion of the delayed rectifier potassium current.[37] This current is affected by a potassium channel that is controlled by the human *ether-a-go-go-related* gene (*HERG*).[35] One study that assessed the interactions between fluoroquinolones and this potassium channel found that sparfloxacin and grepafloxacin were the most potent antagonists, likely explaining the high incidences of TdP reported with these agents. Moxifloxacin and gatifloxacin showed an intermediate ability to inhibit HERG channel current, while levofloxacin and ciprofloxacin had the least inhibitory effects.[39]

A review of the medical literature estimated the incidence of TdP over a 5 year period as 0.3 cases/10 million prescriptions for ciprofloxacin (95% CI 0.0 to 1.1), 27 cases/10 million prescriptions for gatifloxacin (95% CI 12 to 53), 5.4 cases/10 million prescriptions for levofloxacin (95% CI 2.9 to 9.3), and 0 cases/10 million prescriptions for moxifloxacin (95% CI 0.0 to 26).[40] Gatifloxacin caused significantly more cases of TdP versus ciprofloxacin ($p < 0.001$) or levofloxacin ($p = 0.001$). Levofloxacin was associated with significantly more cases of TdP versus ciprofloxacin ($p < 0.001$). The authors cautioned that the low incidence of QTc interval prolongation with moxifloxacin may have been due to its recent introduction into the market. When the incidences of TdP over a 16 month period after initial Food and Drug Administration (FDA) approval of levofloxacin, gatifloxacin, and moxifloxacin were compared, there were no significant differences between any of the groups. The authors concluded that levofloxacin should be used with caution and gatifloxacin should be avoided in patients with other risk factors for QTc interval prolongation.

Noel et al.[41] compared the effects of high-dose levofloxacin, moxifloxacin, and ciprofloxacin on QTc intervals in 47 healthy adults. In this double-blind, single-dose, crossover trial, subjects were randomly assigned to 1 of 4 treatment sequence groups receiving placebo, levofloxacin 1000 mg, moxifloxacin 800 mg, or ciprofloxacin 1500 mg. Results of the study showed that mean values of QTc 1 hour after moxifloxacin dosing were significantly greater than placebo ($p < 0.05$), while differences between mean QTc values after levofloxacin or ciprofloxacin were not significantly different than differences with placebo. As high doses were used in this study, the results must be extrapolated to the usual lower doses of these commonly used antibiotics. The results of this study are consistent with those of the previously cited study, which showed that moxifloxacin had greater inhibitory effects on HERG channel current than did ciprofloxacin or levofloxacin, but the true clinical significance of these findings is not yet known.

According to more recent data submitted to the FDA by moxifloxacin's manufacturer, the drug caused a QTc interval greater than 500 msec in 3 of 787 (0.4%) patients treated with the medication compared with 1 of 759 (0.1%) patients who received the comparator drugs clarithromycin, cephalexin, cefuroxime axetil, amoxicillin, doxycycline, or metronidazole.[42] The mean degree of QTc interval prolongation with moxifloxacin ± SD in clinical trials was 6 ± 26 msec compared with a mean degree of prolongation of 2 ± 23 msec in patients treated with clarithromycin.

Assessment of the incidence of QTc interval prolongation associated with fluoroquinolones poses a challenging task, given that patients may have risk factors for this condition or organ dysfunction, which can increase the risk for TdP. Elevated serum concentrations of ciprofloxacin, gemifloxacin, and levofloxacin may occur if the doses of these medications are not adjusted based on patients' renal function, while the pharmacokinetics of moxifloxacin have not been studied in patients with severe (Child–Pugh class C) hepatic dysfunction. Additionally, the manufacturers of gemifloxacin, levofloxacin, and moxifloxacin recognize the increased risk for QTc interval prolongation in patients with known risk factors who are receiving these drugs. Thus, package inserts for these drugs recommend their avoidance in patients with known prolongation of the QTc interval, or uncorrected hypokalemia, and in patients receiving class Ia or class III antiarrhythmic agents.[6-8] Gemifloxacin's prescribing information also recommends avoidance of the drug in patients with uncorrected hypomagnesemia.[6]

Central Nervous System Effects

Common central nervous system (CNS)–related adverse effects associated with the fluoroquinolones include dizziness, drowsiness, headache, confusion, and tremors. A more serious, but less frequently reported, CNS adverse effect is seizures.[37,43] It is hypothesized that displacement of GABA, competition with GABA at its receptor site, or interaction with glutamate receptors results in CNS stimulation.[2,3] Structural differences at position 7 of the quinolone nucleus influence an agent's interaction with GABA receptors in the brain.[3] Studies have shown that fluoroquinolones with increased CNS penetration and either an unsubstituted piperazine group at position 7 (such as found in ciprofloxacin) or unsubstituted pyrrolidine group at position 7 may be associated with an increased risk of seizures; case reports of possible gatifloxacin- and levofloxacin-induced seizures have also been published.[44,45]

Proposed risk factors for the development of seizures include electrolyte disturbances, decreased renal function, advanced age, and concomitant treatment with another drug that may lower the seizure threshold.[43] In general, since fluoroquinolones may lower the seizure threshold, clinicians should use any of these agents with caution in patients with a history of seizure disorders or other risk factors that may lower the seizure threshold.[6-9,37,43]

Phototoxicity

Structural differences at positions 1, 5, and 8 of the quinolone nucleus influence an agent's risk for phototoxicity. An increased incidence of phototoxicity has been seen in dihalogenated fluoroquinolones, molecules that contain a methoxy group at position 5, and molecules that have a cyclopropyl or ethyl group at position 1.[3,46,47] As previously mentioned, clinical development of clinafloxacin, a dihalogenated fluoroquinolone with a chlorine atom at position 8, was halted because of findings of increased incidence of phototoxicity and hypoglycemia. It is hypothesized that exposure to light generates reactive oxygen species such as superoxide and hydrogen peroxide that attack cellular lipid membranes and cause tissue damage.[2,48] Compounds with a methoxy group at position 8, such as moxifloxacin, appear to have a lower risk of phototoxicity.

Gemifloxacin also has a low risk of phototoxicity, with a reported incidence of 0.039% in clinical trials.[6] However, the prescribing information of all fluoroquinolones warns of the potential for phototoxicity, most commonly manifested in the form of an exaggerated sunburn reaction. Patients should be counseled to avoid excessive amounts of sunlight or artificial ultraviolet light while taking any fluoroquinolone.[3,6-9,46]

Tendinopathy

Fluoroquinolones rarely produce tendinopathy, which ranges from tendonitis to tendon rupture, most commonly affecting the Achilles tendon.[49] The estimated incidence ranges from 0.14% to 0.4%, although this number may be higher in patients with risk factors for tendinopathy. These risk factors include renal transplantation, renal failure, hemodialysis, age greater than 50 years, use of corticosteroids, diabetes mellitus, gout, hyperparathyroidism, peripheral vascular disease, sports participation, and rheumatic disease.[50,51] The risk of fluoroquinolone-induced tendon rupture may be highest among patients more than 60 years of age and in athletic participants receiving concomitant corticosteroids.[37,52]

Although there has not been a widely accepted identified structural moiety on the quinolone nucleus associated with tendinopathies, one study that assessed the effects of fluoroquinolones in rats suggests that structural differences at position 7 may play a role.[53] This study found that compounds with a methylpiperadinyl group at position 7 caused the highest number of tendon lesions in rats, while those with a piperadinyl group had little or no effect. The mechanism surrounding fluoroquinolone-associated tendinopathy is complex and poorly understood. One hypothesis suggests that these drugs are directly toxic on collagen fibers while another suggests that ischemic processes are involved. Fluoroquinolone use may also result in the formation of reactive oxygen species that cause tendon damage. This may result in tendon rupture in patients with risk factors that impede tendon repair, such as advanced age or corticosteroid use.[50]

The prescribing information of all fluoroquinolones contains a warning of possible tendon rupture. These drugs should be used with caution in patients with other risk factors for tendinopathy and the doses should be adjusted based on organ function to potentially lower the risk for this adverse effect.[6-9] A fluoroquinolone should be discontinued at the first sign of tendon pain and patients should avoid exercise until tendonitis has been ruled out.[49]

Clostridium difficile-Associated Diarrhea

All antibiotics may alter normal fecal flora, allowing for the overgrowth of *C. difficile*. It has been proposed that antimicrobial agents with anaerobic activity, such as moxifloxacin, inhibit the growth of protective anaerobic flora that colonize the intestine, increasing the potential for *C. difficile* replication.[54] CDAD ranges in severity of symptoms from mild diarrhea to life-threatening pseudomembranous colitis. In addition to antibiotic exposure and use of an agent with anaerobic antimicrobial activity, other risk factors for the development of CDAD include advanced age and hospitalization.[55]

Pépin et al.[56] conducted a retrospective cohort study to identify risk factors for the development of CDAD during a local epidemic. Identified independent risk factors for CDAD included age, duration of hospitalization, previous episode of CDAD, and receipt of fluoroquinolones, cephalosporins, macrolides, clindamycin, or intravenous β-lactam/β-lactamase inhibitors. Fluoroquinolones were most strongly associated with CDAD (adjusted hazard ratio 3.44; 95% CI 2.65 to 4.47) compared with other antibiotics (adjusted hazard ratios from 1.56 to 1.89). When comparing the fluoroquinolones used in this patient population, the adjusted hazard ratio was 2.52 (95% CI 1.68 to 3.79) for levofloxacin and 3.74 (95% CI 2.82 to 4.97) for ciprofloxacin. This observational study suggests an association between the use of fluoroquinolones and the development of CDAD, and a stronger association with the use of ciprofloxacin. There are several studies that support the association between fluoroquinolone use and CDAD, including resistant strains of *C. difficile*,[57-62] while others have shown a lower risk of CDAD with levofloxacin than with β-lactam antibiotics.[63,64]

A case–control study attempted to identify the cause of increased reports of CDAD that coincided with a formulary change from levofloxacin to gatifloxacin.[65] When levofloxacin was on the formulary, 10 of 58 (17%) patients who received it developed CDAD. After the formulary change, 14 of 47 (30%) patients who received gatifloxacin developed CDAD. Given that the incidence of CDAD de-

creased when levofloxacin was returned to the formulary, the authors concluded that the outbreak of CDAD was associated with the use of gatifloxacin.

One observational study at a German hospital found an increased incidence of CDAD when levofloxacin was replaced by moxifloxacin on the formulary.[54] The estimated incidence of CDAD increased from 6% to 33% with this formulary change and decreased by 13% after reinstating levofloxacin on the formulary and reinforcing hygienic practices. As previously mentioned, the investigators suggested that moxifloxacin, with its increased anaerobic activity versus other fluoroquinolones, may inhibit the growth of protective intestinal anaerobic flora, thus promoting the overgrowth of *C. difficile*.

These results conflict with those of a population-based nested case–control study in Ontario that used healthcare databases to determine whether there were any differences in the incidence of community-acquired CDAD.[66] The investigators analyzed data over a 3 year period and did not find any differences in hospitalization for CDAD in outpatients who had been prescribed gatifloxacin or moxifloxacin compared with levofloxacin.

Although it has been hypothesized that a drug with negative effects on intestinal flora may increase the risk of an agent's causing CDAD, there is no recognized structural moiety on the quinolone nucleus that has been identified as increasing this risk and no strong evidence that one fluoroquinolone causes CDAD more or less than the other drugs in the class. Prescribing information for all fluoroquinolones lists CDAD as a potential adverse drug reaction.[6-9]

Summary

Efficacy, safety, and cost shape the clinician's decision as to the appropriate fluoroquinolone for treatment of a particular patient or suitable drug in this class to include on a formulary. True incidences of the less common, but more serious, adverse effects associated with the fluoroquinolones are difficult to determine. To provide safe treatment for patients who need antibiotic therapy, an assessment of the risk-to-benefit ratio may be warranted in the decision to use a fluoroquinolone. Pharmacists should proactively screen for patient-specific risk factors for adverse effects prior to recommending a fluoroquinolone and should review profiles and medical information of patients already receiving a fluoroquinolone. Close monitoring of patients receiving fluoroquinolone therapy may be beneficial in detection of adverse effects.

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References

1. Domagala JM. Structure–activity and structure–side-effect relationships for the quinolone antibacterials. J Antimicrob Chemother 1994;33:685-706.
2. De Sarro A, De Sarro G. Adverse reactions to fluoroquinolones: an overview on mechanistic aspects. Current Medicinal Chem 2001;8:371-84.
3. Rubenstein E. History of quinolones and their side effects. Chemother 2001;47(suppl 3):3-8.
4. Andriole VT. The quinolones: past, present, and future. Clin Infect Dis 2005;41(suppl 2):S113-9.
5. O'Donnell JA, Gelone SP. Fluoroquinolones. Infect Dis Clin North Am 2000;14:489-513.
6. Package insert. Factive (gemifloxacin). Waltham, MA: Oscient Pharmaceuticals Corporation, August 2005.
7. Package insert. Levaquin (levofloxacin). Raritan, NJ: Ortho-McNeil Pharmaceutical, Inc., April 2007.
8. Package insert. Avelox (moxifloxacin). West Haven, CT: Bayer Pharmaceuticals Corporation, October 2006.
9. Package insert. Cipro (ciprofloxacin). West Haven, CT: Bayer Pharmaceuticals Corporation, December 2005.
10. Owens RC. Fluoroquinolone-associated dysglycemias: a tale of two toxicities. Pharmacotherapy 2005;25:1291-5.
11. Shilo S, Berezovsky S, Friedlander Y, Sonnenblick M. Hypoglycemia in hospitalized nondiabetic older patients. J Am Geriatr Soc 1998;46:978-82.
12. Kagansky N, Levy S, Rimon E, et al. Hypoglycemia as a predictor of mortality in hospitalized elderly patients. Arch Intern Med 2003;163:1825-9.
13. Mohr JF, McKinnon PG, 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.
14. Lomaestro BM, Lodise TP. Comparison of glucose intolerance between gatifloxacin and piperacillin–tazobactam in elderly, hospitalized patients. Presented at: the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, October 30–November 2, 2004.
15. Coblio NA, Mowrey K, McCright P, Means H, McCormick MT. Use of a data warehouse to examine the effect of fluoroquinolones on glucose metabolism. Am J Health Syst Pharm 2004;61:2545-8.
16. LeBlanc M, Belanger C, Cossette P. Severe and resistant hypoglycemia associated with concomitant gatifloxacin and glyburide therapy. Pharmacotherapy 2004;24:926-31.
17. 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.
18. Baker SE, Hangii MC. Possible gatifloxacin-induced hypoglycemia. Ann Pharmacother 2002;36:1722-6. DOI 10.1345/aph.1A480
19. Biggs WS. Hypoglycemia and hyperglycemia associated with gatifloxacin use in elderly patients. J Am Board Fam Pract 2003;16:455-7.
20. Happe MR, Mulhall BP, Maydonovitch CL, Holtzmuller KC. Gatifloxacin-induced hyperglycemia. Ann Intern Med 2004;141:968-9.
21. Beste LA, Mersfelder TL. Hyperglycemia and gatifloxacin: a case report and summary of current literature. Am J Geriatr Pharmacother 2005;3:262-5.
22. Frothingham R. Glucose homeostasis abnormalities associated with use of gatifloxacin. Clin Infect Dis 2005;41:1269-76.
23. Park-Wyllie LY, Juurlink DN, Kopp A, et al. Outpatient gatifloxacin therapy and dysglycemia in older adults. N Engl J Med 2006;354:1352-61.
24. Gatifloxacin (marketed as Tequin): information for healthcare professionals. Food and Drug Administration. www.fda.gov/cder/drug/InfoSheets/HCP/gatifloxacinHCP.pdf (accessed 2007 May 23).
25. Drug shortages?—discontinuations. Food and Drug Administration, Centers for Biologics Evaluation and Research. www.fda.gov/cder/drug/shortages/ TequinDiscontinuation2006.pdf (accessed 2007 May 23).

26. Saraya A, Yokokura M, Gonoi T, Seino S. Effects of fluoroquinolones on insulin secretion and β-cell ATP-sensitive K+ channels. Eur J Pharmacol 2004;497:111-7. DOI 10.1016/j.ejphar.2004.06.032
27. Graumlich JF, Habis S, Avelino RR, et al. Hypoglycemia in inpatients after gatifloxacin or levofloxacin therapy: nested case–control study. Pharmacotherapy 2005;25:1296-302.
28. Roberge RJ, Kaplan R, Frank R, Fore C. Glyburide–ciprofloxacin interaction with resistant hypoglycemia. Ann Emerg Med 2000;36:160-3. DOI 10.1067/mem.2000.108617
29. Lin G, Hays DP, Spillane L. Refractory hypoglycemia from ciprofloxacin and glyburide interaction. J Toxicol Clin Toxicol 2004;42:295-7. DOI 10.1081/CLT-120037431
30. Friedrich LV, Dougherty R. Fatal hypoglycemia associated with levofloxacin. Pharmacotherapy 2004;24:1807-12.
31. Kanbay M, Aydogan T, Bozalan R, et al. A rare but serious side effect of levofloxacin: hypoglycemia in a geriatric patient (letter). Diabetes Care 2006;29:1716-7. DOI 10.2337/dc06-0788
32. Wang S, Rizvi AA. Levofloxacin-induced hypoglycemia in a nondiabetic patient. Am J Med Sci 2006;331:334-5.
33. Gavin JR 3rd, Kubin R, Choudhri S, et al. Moxifloxacin and glucose homeostasis: a pooled-analysis of the evidence from clinical and postmarketing studies. Drug Saf 2004;27:671-86.
34. 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. DOI 10.1093/jac/dkg370
35. Roden DM. Drug-induced prolongation of the QT interval. N Engl J Med 2004;350:1013-22.
36. Owens RC Jr. Risk assessment for antimicrobial agent–induced QTc prolongation and torsades de pointes. Pharmacotherapy 2001;21:310-9.
37. Owens RC, Ambrose PG. Antimicrobial safety: focus on fluoroquinolones. Clin Infect Dis 2005;41(suppl 2):S144-57.
38. Iannini PB, Tillotson GS. Evaluating the risk of cardiac toxicity. Pharmacotherapy 2001;21:261-2.
39. Kang J, Wang L, Chen XL, Triggle DJ, Rampe D. Interactions of a series of fluoroquinolone antibacterial drugs with the human cardiac K+ channel HERG. Mol Pharmacol 2001;59:122-6.
40. Frothingham R. Rates of torsades de pointes associated with ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, and moxifloxacin. Pharmacotherapy 2001;21:1468-72.
41. 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. DOI 10.1016/S0009-9236(03)00009-2
42. FDA resources page. www.fda.gov/ohrms/dockets/ac/99/slides/3558s1i.ppt (accessed 2007 Aug 6).
43. Kushner JM, Peckman HJ, Snyder CR. Seizures associated with fluoroquinolones. Ann Pharmacother 2001;35:1194-8. DOI 10.1345/aph.10359
44. Quigley CA, Lederman JR. Possible gatifloxacin-induced seizure. Ann Pharmacother 2004;38:235-7. DOI 10.1345/aph.1D349
45. Christie MJ, Wong K, Ting RH, Tam PY, Sikaneta TG. Generalized seizure and toxic epidermal necrolysis following levofloxacin exposure. Ann Pharmacother 2005;39:953-5. Epub 12 Apr 2005. DOI 10.1345/aph.1E587
46. Ball P, Mandell L, Niki Y, Tillotson G. Comparative tolerability of the newer fluoroquinolone antibacterials. Drug Saf 1999;21:407-21.
47. 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.
48. Mayne JT, Johnson NJ, Kluwe WM, Lencoski DL, Polzer RJ. A study of the phototoxic potential of trovafloxacin in BALB/c mice. J Antimicrob Chemother 1997;39(suppl B):67-73.
49. Lipsky BJ, Baker C. Fluoroquinolone toxicity profiles: a review focusing on newer agents. Clin Infect Dis 1999;28:352-64.
50. Khaliq Y, Zhanel GG. Fluoroquinolone-associated tendinopathy: a critical review of the literature. Clin Infect Dis 2003;36:1404-10.
51. van der Linden PD, van Puijenbroek EP, Feenstra J, et al. Tendon disorders attributed to fluoroquinolones: a study on 42 spontaneous reports in the period 1988 to 1998. Arthritis Care Res 2001;45:235-9.
52. 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.
53. Kashida Y, Kato M. Characterization of fluoroquinolone-induced Achilles tendon toxicity in rats: comparison of toxicities of 10 fluoroquinolones and effects of anti-inflammatory compounds. Antimicrob Agents Chemother 1997;41:2389-93.
54. von Baum H, Sigge A, Bommer M, et al. Moxifloxacin prophylaxis in neutropenic patients. J Antimicrob Chemother 2006;58:891-4. DOI 10.1093/jac/dk1320
55. Bartlett JG. Antibiotic-associated diarrhea. N Engl J Med 2002;346:334-9.
56. Pépin J, Saheb N, Coulombe MA, et al. Emergence of fluoroquinolones as the predominant risk factor for *Clostridium difficile*–associated diarrhea: a cohort study during an epidemic in Quebec. Clin Infect Dis 2005;41:1254-60.
57. Yip C, Loeb M, Salama S, Moss L, Olde J. Quinolone use as a risk factor for nosocomial *Clostridium difficile*–associated diarrhea. Infect Control Hosp Epidemiol 2001;22:572-5.
58. Muto CA, Pokrywka M, Shutt K, et al. A large outbreak of *Clostridium difficile*–associated disease with an unexpected proportion of deaths and colectomies at a teaching hospital following increased fluoroquinolone use. Infect Control Hosp Epidemiol 2005;26:273-80.
59. McCusker ME, Harris AD, Perencevich E, Roghmann MC. Fluoroquinolone use and *Clostridium difficile*–associated diarrhea. Emerg Infect Dis 2003;9:730-3.
60. Drudy D, Quinn T, O'Mahony R, Kyne L, O'Gaora P, Fanning S. High-level resistance to moxifloxacin and gatifloxacin associated with a novel mutation in gyrB in toxin-A–negative, toxin-B–positive *Clostridium difficile*. J Antimicrob Chemother 2006;58:1264-7. DOI 10.1093/jac/dk1398
61. Kazakova SV, Ware K, Baughman B, et al. A hospital outbreak of diarrhea due to an emerging epidemic strain of *Clostridium difficile*. Arch Intern Med 2006;166:2518-24.
62. Loo VG, Poirier L, Miller MA, et al. A predominantly clonal multi-institutional outbreak of *Clostridium difficile*–associated diarrhea with high morbidity and mortality. N Engl J Med 2005;353:2442-9.
63. Rao GC, Rao CSM, Starke I. *Clostridium difficile*–associated diarrhoea in patients with community-acquired lower respiratory infection being treated with levofloxacin compared with β-lactam–based therapy. J Antimicrob Chemother 2003;51:697-701. DOI 10.1093/jac/dkg115
64. Mendez MN, Gibbs L, Jacobs RA, McCulloch CE, Winston L, Gugleilmo BJ. Impact of a piperacillin–tazobactam shortage on antimicrobial prescribing and rate of vancomycin-resistant enterococci and *Clostridium difficile* infections. Pharmacother 2006;26:61-7.
65. Gaynes R, Rimland D, Killum E, et al. Outbreak of *Clostridium difficile* infection in a long-term care facility: association with gatifloxacin use. Clin Infect Dis 2004;38:640-5.
66. Dhalla IA, Mamdani MM, Simor AE, Kopp A, Rochon PA, Juurlink DN. Are broad-spectrum fluoroquinolones more likely to cause *Clostridium difficile*–associated disease? Antimicrob Agents Chemother 2006;50:3216-9. DOI 10.1128/AAC.00592-06

Un Análisis de las Inquietudes de las Fluoroquinolonas

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EXTRACTO

OBJETIVO: Analizar la química, la farmacología, y la seguridad de la clase de antibióticos fluoroquinolonas.

FUENTES DE DATOS: Se llevó a cabo una búsqueda en MEDLINE de los artículos publicados en inglés (1966–julio 2007) usando las palabras

clave fluoroquinolonas o quinolonas junto con seguridad, efectos adversos, hipoglucemia, hiperglucemia, disglucemia, prolongación del QTc, torsades, convulsiones, fototoxicidad, ruptura de tendones, *Clostridium difficile*, y colitis seudomembranosa.

SELECCIÓN DE ESTUDIOS Y MÉTODO DE EXTRACCIÓN DE LA INFORMACIÓN: Se revisó la química médica, los ensayos in vitro, en animales y en humanos para obtener información sobre la química, la farmacología, y la seguridad de cada fluoroquinolona. Se analizaron y se incluyeron los ensayos clínicos para comparar la seguridad de las fluoroquinolonas sistémicas existentes actualmente en el mercado. También se revisó la literatura concerniente a la patología de los efectos adversos graves.

SÍNTESIS DE LOS DATOS: Se ha demostrado que el gatifloxacino incrementa el riesgo de hospitalización por disglucemia en pacientes con y sin diabetes. La hiperglucemia puede aparecer con cualquier fluoroquinolona, especialmente, si no se ha ajustado adecuadamente la dosis. La hipoglucemia puede ocurrir también con cualquier fluoroquinolona y es más frecuente en los pacientes que reciben un tratamiento concomitante con hipoglucemiantes orales o con insulina. Las fluoroquinolonas deberían evitarse en los pacientes que presentan factores de riesgo para la prolongación del QTc o para sufrir tendinopatías. Todas las fluoroquinolonas han de usarse con precaución en los pacientes que han sufrido convulsiones; además pueden causar potencialmente fototoxicidad o diarrea asociada a *Clostridium difficile*.

CONCLUSIONES: Los médicos deberían estar atentos a cualquier cambio que pudiera ocurrir en los niveles sanguíneos de glucosa, en el intervalo QTc, si hubiese convulsiones o apareciese fototoxicidad, tendinopatías, o diarrea asociada a *Clostridium difficile* tras el uso de cualquier fluoroquinolona, especialmente en pacientes con otros factores de riesgo para estas patologías. Los médicos han de controlar estrechamente estos efectos adversos y ajustar adecuadamente la dosis de fármacos específicos para minimizar los riesgos. Se debe evaluar el cociente beneficio-riesgo antes de usar las fluoroquinolonas para proporcionar así un tratamiento seguro a los pacientes que requieran antibióticos.

Traducido por Violeta Lopez Sanchez

Revue de l'Innocuité des Fluoroquinolones

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RÉSUMÉ

OBJECTIF: Revoir la chimie, la pharmacologie, et l'innocuité des antibiotiques de la classe des fluoroquinolones.

REVUE DE LITTÉRATURE: Une recherche informatisée MEDLINE couvrant la période de 1966–juillet 2007 fut effectuée pour identifier les articles publiés en anglais en utilisant les mots clés suivants: fluoroquinolones ou quinolones avec innocuité, effets secondaires, hypoglycémie, hyperglycémie, dysglycémie, prolongation de l'onde QTc, torsades, convulsions, phototoxicité, rupture de tendon, *Clostridium difficile*, et colite pseudomembraneuse.

SÉLECTION DES ÉTUDES ET DE L'INFORMATION: Les données de chimie médicinale ainsi que les études in vitro, animales, et humaines furent revisées relativement à l'information sur la chimie, la pharmacologie, et l'innocuité de chaque fluoroquinolone. Les études cliniques furent revisées pour évaluer l'innocuité des fluoroquinolones commercialement disponibles. La littérature sur la pathologie des effets secondaires sérieux est également présentée.

RÉSUMÉ: La gatifloxacine a été démontrée comme augmentant le risque d'hospitalisation pour dysglycémie chez des patients avec ou sans diabète. L'hyperglycémie peut survenir avec n'importe quelle fluoroquinolone, particulièrement si la dose n'est pas ajustée. L'hypoglycémie peut également survenir avec n'importe quelle fluoroquinolone mais semble plus fréquente auprès des patients recevant un hypoglycémiant oral ou de l'insuline. L'utilisation de toute fluoroquinolone devrait être évitée chez les patients présentant des facteurs de risque pour le prolongement de l'onde QTc ou tendinopathie. Toutes les fluoroquinolones devraient être utilisées avec précaution chez les patients présentant une histoire de convulsions. De plus, elles peuvent potentiellement causer de la phototoxicité et de la diarrhée associée au *Clostridium difficile*.

CONCLUSIONS: Les cliniciens devraient porter une attention particulière aux altérations de la glycémie, au prolongement de l'intervalle QTc, aux convulsions, à la phototoxicité, à la tendinopathie, et à la diarrhée associée au *Clostridium difficile*, spécialement chez les patients présentant d'autres facteurs de risque pour ces mêmes conditions. Les cliniciens devraient monitorer ces effets secondaires et ajuster la dose de chaque agent de façon à réduire les risques d'occurrence de tels effets. Une évaluation du ratio risque-bénéfice devrait être amorcée chaque fois que la décision de choisir une fluoroquinolone est prise.

Traduit par Marc M Perreault