

Using Safety Profiles to Differentiate between the Newer Fluoroquinolones

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Fluoroquinolones are considered safe and well-tolerated anti-infective agents. Among the newer agents (e.g., levofloxacin, moxifloxacin, gemifloxacin, gatifloxacin), the safety profiles continue to be evaluated. High-dose levofloxacin (750 mg once-daily) for short-course therapy or serious infections has demonstrated excellent tolerability and rates of adverse events comparable with other newer fluoroquinolones. Recent studies evaluating moxifloxacin 400 mg once-daily have demonstrated a similar safety profile to levofloxacin 500 mg once-daily in elderly patients treated for community-acquired pneumonia. However, prolongation of the QTc interval occurs more frequently with moxifloxacin than with levofloxacin. Skin rash remains the major limitation in the safety profile of gemifloxacin and has restricted the duration of therapy to 5 or 7 days. Gemifloxacin-associated rash most commonly occurs after 8 to 10 days of therapy, in female patients younger than 40 years of age, and postmenopausal women receiving hormone replacement therapy. The increasing number of reports and higher incidence of hypoglycemia and hyperglycemia with gatifloxacin compared with other antibiotic therapy, including fluoroquinolones, has resulted in governmental agencies placing a contraindication on the use of gatifloxacin in patients with diabetes.

Introduction

Fluoroquinolones are considered safe and well-tolerated anti-infective agents that are commonly used to treat community-acquired and healthcare-associated infections (1–5). The most frequent reported adverse events (eg., gastrointestinal,

central nervous system, and dermatological reactions) are usually transient and mild to moderate in severity (Table 1) (2, 6–9). However, rare and agent-specific serious adverse reactions do occur, and have led to restrictive use or withdrawal of several fluoroquinolones (e.g., trovafloxacin,

Table 1. Comparative adverse events and discontinuation rates for selected fluoroquinolones*

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

* data presented as percentages
Adapted from references (2, 6–9).

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temafloxacin, grepafloxacin) (10–12). The purpose of this paper is to review the most recent studies evaluating the safety profile of newer fluoroquinolones (e.g., levofloxacin, moxifloxacin, gemifloxacin). In addition, a comprehensive appraisal of the hypo/hyperglycemic effects of gatifloxacin will be addressed.

Levofloxacin

Levofloxacin has an established safety profile for a broad range of clinical indications. The initial FDA-approved clinical indications for levofloxacin included a 250 mg once-daily dose for the treatment of urinary tract infections, and a 500 mg once-daily dose for uncomplicated skin and skin structure infections, acute bacterial exacerbation of chronic bronchitis, community-acquired pneumonia, acute maxillary sinusitis, and chronic bacterial prostatitis (6). Subsequently, a higher dose (eg., 750 mg once-daily) of levofloxacin was approved for the treatment nosocomial pneumonia and complicated skin and skin structure infections (13, 14). Comparable rates of treatment-emergent, drug-related, and serious adverse effects have been demonstrated regardless of which once-daily dosing regimen (250 mg, 500 mg or 750 mg) of levofloxacin is used (6).

The focus of the most recent efficacy and safety studies of levofloxacin has been on short-course (5 days or less) therapy with the 750 mg once-daily dose. In multicenter, noninferiority studies involving adults with either community-acquired pneumonia or acute bacterial sinusitis, a short course of 750 mg levofloxacin once daily for 5 days was well tolerated and as effective as the traditional 10-day course of levofloxacin 500 mg (15, 16). No significant differences in drug-related adverse events were demonstrated when these two dosage regimens were compared in a combined analysis of these clinical studies (17). A similar safety profile has also been demonstrated for short courses (eg., 3 or 5 days) of levofloxacin 750 mg for the treatment of acute bacterial exacerbations of chronic bronchitis (18).

Moxifloxacin

Several recent studies have compared the efficacy and safety profiles of moxifloxacin and levofloxacin in patients being treated for lower respiratory tract infections (19–21). A prospective, randomized, double-blind study compared moxifloxacin 400 mg once-daily for 5 days and levofloxacin 500 mg once-daily for 7 days for the treatment of patients with acute exacerbations of chronic bronchitis in Latin America (19). The clinical (91.0% [$n = 221$] vs 94.0% [$n = 216$]) and microbiological (92.8% [$n = 138$] vs 93.8% [$n = 129$])

success rates for moxifloxacin versus levofloxacin were similar. The most common adverse events that were possibly or probably related to moxifloxacin versus levofloxacin therapy were nausea (4.3% vs 5.7%), diarrhea (2.9% vs 2.8%), headache (2.5% vs 1.4%), dizziness (0.7% vs 0.7%), somnolence (1.1% vs 0.7%), and insomnia (0.4% vs 1.4%). Each fluoroquinolone was associated with a single serious adverse event report that was considered possibly (dyspnea for moxifloxacin) or probably (upper gastrointestinal tract bleeding for levofloxacin) related to the study drug. Overall, therapy with either fluoroquinolone was well tolerated, and the rate of discontinuation of therapy because of adverse events was less than 2%.

Anzueto et al. reported the clinical and safety results of the Community-Acquired Pneumonia Recovery in the Elderly (CAPRIE) study group (20). This study was a prospective, randomized, double-blind study comparing moxifloxacin 400 mg once-daily versus levofloxacin 500 mg once-daily therapy for the treatment of community-acquired pneumonia in 394 elderly patients. The test-of-cure rates for patients treated with moxifloxacin and levofloxacin were similar and did not differ based on age (e.g., 90.0% and 85.0% ($p = 0.6$) for 65–74 years of age and 94.5% and 90.0% ($p = 0.4$) for ≥ 75 years of age). The rates of serious adverse events and drug-related adverse events were similar for these two fluoroquinolones. However, a higher rate of treatment-emergent adverse events was reported for moxifloxacin versus levofloxacin (84.1% vs 73.4%, $p = 0.01$). The most frequent drug-related adverse events reported in $> 1.5\%$ of patients were nausea, diarrhea, oral candidiasis, *Clostridium difficile* infection, and cardiac events.

In a separate report, Morganroth et al. evaluated the cardiac rhythm safety of moxifloxacin and levofloxacin in patients from the CAPRIE study. The mean QTc changes in the moxifloxacin- and levofloxacin-treated patients on day three of therapy were $+6.4 \pm 23.2$ ms and -2.5 ± 22.9 ms ($p = 0.04$) and $+5.3 \pm 23.7$ ms and -5.1 ± 25.8 ms ($p = 0.03$) based on the Fridericia and Bazett formulas, respectively. These results confirm several previous studies showing moxifloxacin 400 mg increases the QTc interval by 6 to 12 msec whereas levofloxacin 500 mg is not associated with an increase in the QTc interval (21–27). In addition, the recommended dose (eg., 400 mg once-daily) or intravenous infusion rate (eg., 60-minutes) of moxifloxacin should not be exceeded since the effects on prolongation of QTc interval are dose- and/or concentration-dependent (8, 25). Identification of risk factors for QTc interval prolongation and *torsades de pointes*

for fluoroquinolones such as moxifloxacin must be carefully evaluated before being prescribed in susceptible patient populations (28–32).

Gemifloxacin

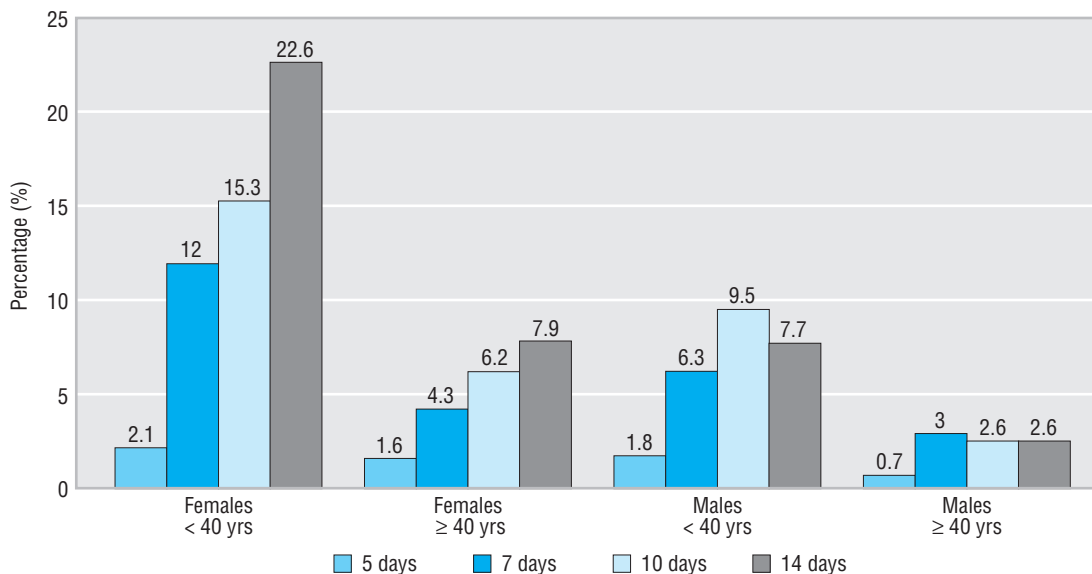
The safety profile of gemifloxacin has recently been reviewed in several reports and at an FDA–Anti-infective Drugs Advisory Committee meeting (33–35). In 6,775 patients who received oral gemifloxacin 320 mg once-daily, treatment-related adverse events were reported in 1,179 (17.4%) with the most frequent adverse events being diarrhea (3.6%), rash (2.8%), and nausea (2.7%) (33). These same adverse events occurred in 4.6%, 0.6%, and 3.2%, respectively, of the 5,248 patients receiving a comparator agent. Discontinuation of therapy because of adverse drug reactions occurred in 2.2% and 2.1% of patients receiving gemifloxacin and comparator agent, respectively. In the gemifloxacin group, the appearance of the maculopapular rash (0.9% of all patients) was the most common adverse cause for discontinuation of therapy. Other serious adverse events (e.g., phototoxicity, musculoskeletal syndromes, QT interval prolongation and cardiac rhythm problems, hepatic and hematological changes, hypo-/hyperglycemia) associated with specific fluoroquinolones have not been commonly reported with gemifloxacin (33).

The gemifloxacin-related rash has most commonly been described as a maculopapular, exanthematous (morbilliform) skin reaction (33–35). The rash usually develops on the upper trunk,

and occasionally on the extremities. Pruritus was reported in only 15% of patients and it usually did not respond to antihistamine or corticosteroid therapy. The rash has not been associated with eosinophilia or severe or toxic manifestations (eg., Stevens–Johnson syndrome, mucous erythema multiform, toxic epidermal necrolysis). The severity of gemifloxacin-related rash has usually been described as mild to moderate, however up to 10% of patients have experienced a rash judged as severe. The rash usually resolves in 60% and 80% of patients within 7 and 14 days after discontinuing gemifloxacin therapy, respectively (9). The rash most commonly occurs after 8 to 10 days of therapy, in female patients less than 40 years of age, and postmenopausal women receiving hormone replacement therapy (Figure 1). The incidence of rash increases with the number of days of therapy: 1.2% at 5 days, 5.3% at 7 days, and 7.4% at 14 days of therapy. Prolonged therapy (eg., greater than 7 days) should be avoided, and gemifloxacin should be discontinued in patients who develop a rash.

A double-blind, double dummy, crossover study was conducted in healthy female subjects < 40 years of age to further characterize the gemifloxacin-associated rash (33–35). Female subjects were randomized in a 5:1 ratio to receive oral gemifloxacin 320 mg once-daily or ciprofloxacin 500 mg twice-daily for 10 days or until a rash developed. Rash developed in 260 of 819 (31.7%) and seven of 164 (4.3%) subjects receiving gemifloxacin and ciprofloxacin, respectively.

Figure 1. Incidence of gemifloxacin-associated skin rash categorized by sex, age, and duration of therapy



Adapted from reference (15).

The onset of gemifloxacin-associated rash occurred between 8 and 10 days (median: 9 days; range: 1 to 17 days) in 82% of subjects respectively. The majority (> 80%) of the rashes were maculopapular, with a median duration of 6 days. The rashes were considered mild, moderate and severe in 62%, 31%, and 7% of subjects. The second part of this study allowed subjects to be re-randomized to placebo or the opposite treatment regimen at 4 to 6 weeks after the initial dosing period. The rate of rash (cross-sensitization) in subjects who initially experienced a gemifloxacin-associated rash and then received ciprofloxacin was 10.4% (15 of 144 subjects). In comparison, the rate of rash in subjects who did not experience a ciprofloxacin-associated rash and then received a second course of ciprofloxacin was 4.9% (7 of 144). In subjects who did not experience a gemifloxacin-associated rash, subsensitization was low since rash developed in only 7 of 258 (2.7%) placebo-treated subjects and 8 of 250 (3.2%) subjects receiving a second course of gemifloxacin.

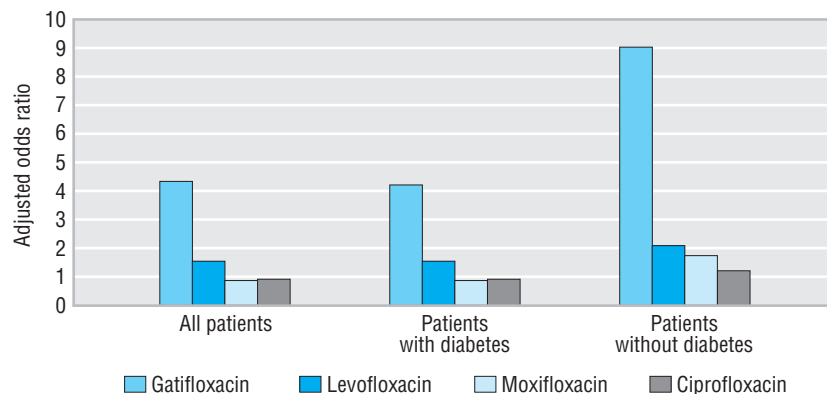
The executive summary of a recent Anti-Infective Drugs Advisory Committee outlined the current issues that the FDA has with regard to gemifloxacin-associated rash: 1) a higher rate of rash with gemifloxacin versus all other comparator agents, including other fluoroquinolones; 2) the potential of cross-sensitization to other fluoroquinolones; 3) the potential for a patient be inappropriately labeled as “fluoroquinolone-allergic” and which may limit the use of other fluoroquinolones when needed; and 4) the unlikelihood of clinicians limiting the duration of gemifloxacin therapy to 5 or 7 days (35). In addition, the FDA expressed concerns regarding the potential for hepatic toxicity of gemifloxacin at a dose of 640 mg.

Gatifloxacin

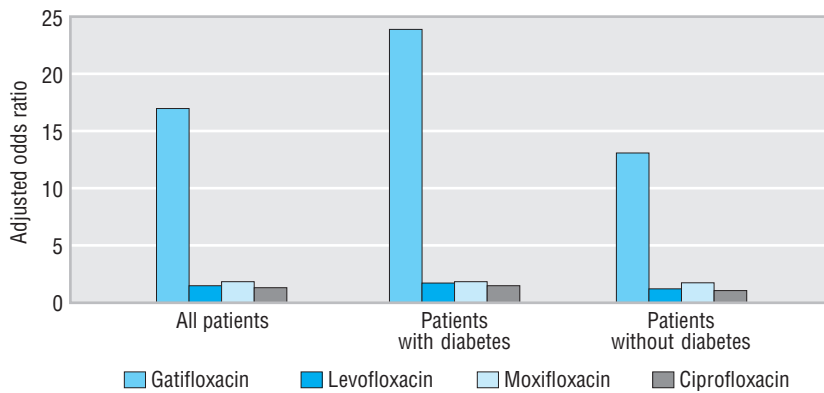
Since 2002, there have been numerous case reports, retrospective studies, and post-marketing surveillance reports that have indicated that hypoglycemia and hyperglycemia occur more often with gatifloxacin than with other commonly used antimicrobial agents, including fluoroquinolones (7, 36–53). Park-Wyllie et al. reported two nested case-control studies that examined the risk of hypoglycemia and hyperglycemia associated with antibiotic treatment (a fluoroquinolone [gatifloxacin, levofloxacin, moxifloxacin, ciprofloxacin], a macrolide [erythromycin, clarithromycin, azithromycin] or a second-generation cephalosporin [cefuroxime axetil or cefaclor]) in Canadian patients who were > 65 years of age (36). Among 788 elderly patients, gatifloxacin was associated with a significantly increased risk (adjusted odds ratio [AOD]: 4.3; 95 percent confidence interval [CI]: 2.9 to 6.3) of hypoglycemia within 30 days after therapy when compared with macrolide therapy. A comparison of the adjusted odds ratio of the four fluoroquinolones in patients with and without diabetes is displayed in Figure 2. In 470 elderly patients, gatifloxacin was also associated with an increased risk (AOD: 16.7; CI: 10.4 to 26.8) of hyperglycemia compared with macrolide therapy. No risk of hyperglycemia within 30 days after antibiotic therapy was seen with the other fluoroquinolones (Figure 3) or a cephalosporin. The risk for gatifloxacin-associated hypoglycemia and hyperglycemia was similar for patients with and without diabetes. The median time from the start of gatifloxacin therapy to hospital admission was 6 and 5 days for hypoglycemia and hyperglycemia, respectively.

Graumlich et al. evaluated the incidence of hypoglycemia (defined as a blood glucose concen-

Figure 2. Adjusted odds ratios associated with hypoglycemia-related hospital visits and fluoroquinolone use



Adapted from reference (36).

Figure 3. Adjusted odds ratios associated with hyperglycemia-related hospital visits and fluoroquinolone use

Adapted from reference (36).

tration < 51 mg/dL) among 7,287 hospitalized patients receiving either gatifloxacin or levofloxacin. The 12-month incidence of hypoglycemia for patients receiving levofloxacin and gatifloxacin was 11/1,000 patients and 21/1,000 patients, respectively (absolute risk increase of 10/1,000 patients; CI: 4–16/1,000). Renal impairment, sepsis syndrome, and concomitant hypoglycemia drug therapy were also significantly associated with hypoglycemia. After adjusting for these significant covariates, gatifloxacin had an increased risk (AOD: 2.81; CI: 1.02 to 7.70) of hypoglycemia compared with levofloxacin (37).

Mohr et al. conducted a retrospective study to compare the rates of dysglycemia in 17,108 hospitalized patients receiving either gatifloxacin, levofloxacin, ciprofloxacin, or ceftriaxone (38). Dysglycemia was defined as serum glucose concentrations < 50 mg/dL or > 200 mg/dL within 72 hours of antibiotic therapy. A total of 101 patients had dysglycemia: 9 (9%) being hypoglycemic and 92 (91%) hyperglycemic. The relative risks of dysglycemia for gatifloxacin, levofloxacin, ciprofloxacin, and ceftriaxone were 1.01% (76 of 7,540 patients), 0.93% (11 of 1,179 patients), 0% (545 patients), and 0.18% (14 of 7,844 patients), respectively. No difference in the rate of dysglycemia was found between gatifloxacin and levofloxacin (relative risk [RR]: 1.07; CI: 0.62 to 1.86), however the rate of dysglycemia was higher in patients receiving a fluoroquinolone versus ceftriaxone (RR: 3.32; CI: 2.31 to 4.78). Concomitant sulfonylurea therapy was the only independent risk factor in patients experiencing hypoglycemia and receiving a fluoroquinolone compared with patients who had hyperglycemia.

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 (39). Gatifloxacin accounted for 80% (453 of 568) of all adverse event reports for glucose homeostasis abnormalities, and 68% (17 of 25) of the reported fatalities. In addition, glucose homeostasis reactions accounted for 24% of all reported adverse event reports for gatifloxacin compared with 1.3%, 1.6%, and 1.3% for ciprofloxacin, levofloxacin, and moxifloxacin, respectively. The reasons why gatifloxacin is associated with a higher frequency of blood glucose disturbances 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 (54–58). *In vitro* studies support the clinical findings that temofloxacin and gatifloxacin have a much greater potential to induce these changes compared with levofloxacin or moxifloxacin.

Following the most recent series of reports regarding the gatifloxacin-associated hypoglycemia and hyperglycemia reactions, the labeling of the FDA-approved product package insert for gatifloxacin has been changed (Table 2) (7). The FDA (as well as Health Canada) has advised that gatifloxacin is contraindicated in patients with diabetes (7). Similar to previous reports, the hypoglycemic reactions tended to occur in diabetic patients while hyperglycemic episodes occurred in patients not previously diagnosed with diabetes. In addition, caution needs to be exercised when prescribing gatifloxacin for patients who are elderly. This latter recommendation is supported, in part, by the observations that elderly patients (eg., ≥ 65 years) are at an increased risk of severe hyperglycemia secondary to age-related decreases

Table 2. Updated warning statements regarding gatifloxacin (Tequin®) and disturbances in blood glucose

“Disturbances of blood glucose, including symptomatic hypoglycemia and hyperglycemia, have been reported with Tequin, usually in diabetic patients, however, hypoglycemia and particularly hyperglycemia have occurred in patients without a history of diabetes. In addition to diabetes, other risk factors associated with dysglycemia while taking Tequin included older age, renal insufficiency, and concomitant glucose-altering medications (particularly hypoglycemic medications). Patients with risk factors should be closely monitored for glucose disturbances. If signs and symptoms of either hypoglycemia or hyperglycemia occur in any patient being treated with Tequin, appropriate therapy must be initiated immediately and Tequin should be discontinued.”

“During the post marketing period, there have been very rare reports of serious disturbances of glucose homeostasis in patient treated with Tequin. These include hyperosmolar non-ketotic hyperglycemic coma, diabetic ketoacidosis, hypoglycemic coma, convulsions and mental status changes (including loss of consciousness). Most of these events were reversible when appropriately managed, although a few resulted in fatal outcome.”

Source: Product package insert for gatifloxacin (7).

in renal function and higher serum gatifloxacin concentrations (59). Further studies are needed to determine whether hyperglycemia can be avoided by using a lower dose of gatifloxacin (eg., 200 mg/day).

Glucose Homeostasis Reactions and Fluoroquinolones

The incidence of glucose homeostasis reactions (eg., hypoglycemia and hyperglycemia) with the other currently available fluoroquinolones is considered extremely low (eg., less than 2%) (60). The product package inserts outline the potential for symptomatic hypoglycemic and/or hyperglycemic reactions (6–9). 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 (eg., glyburide or glibenclamide). Careful monitoring of blood glucose is recommended in patients at risk of these reactions, and fluoroquinolone therapy should be discontinued and appropriate treatment started immediately if a hypoglycemic reaction occurs.

It does appear that some fluoroquinolones are 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 hypoglycemic events during Phase II and III clinical trials was much higher in patients treated with clinafloxacin versus comparator agents (4.0% versus 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 (61). As previously discussed above, hypoglycemia and hyperglycemia occur more often with gatifloxacin than with other commonly used antimicrobial agents, including fluoroquinolones (7, 36–53).

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