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Dysglycemia and fluoroquinolones: Are you putting patients at risk?

Consider an alternative in patients with specific risk factors

Martin Catero, MD
Scottsdale Healthcare Family Medicine Residency Program, Scottsdale, Ariz

Practice recommendations

- Avoid giving gatifloxacin to patients.
- Consider selecting an antibiotic other than a fluoroquinolone for an elderly patient with diabetes mellitus (especially those taking sulfonylureas), hepatic insufficiency, or renal insufficiency (**A**).
- Discontinue fluoroquinolone therapy if a patient experiences symptoms of hypo- or hyperglycemia, or if blood glucose levels fall below 60 mg/dL or rise above 200 mg/dL (**C**).

When was the last time you checked a glucose level before prescribing a fluoroquinolone? Though most side effects of these drugs are mild and self-limited (nausea, anorexia, vomiting, abdominal pain, diarrhea, taste disturbance, dizziness, headache, and somnolence), dysglycemia—hypo- or hyperglycemia—is another side effect that is potentially fatal.

From their inception, fluoroquinolones were known to upset glucose metabolism. However, recent publication of several case reports of gatifloxacin-associated dysglycemia, and Bristol-Myers Squibb's announcement of a contraindication for gatifloxacin in diabetic patients, brought the matter of potentially severe dysglycemia to the forefront.[1]

This article reviews the available literature on fluoroquinolone-associated dysglycemia—first describing the frequency of dysglycemic events and then discussing the possible causes of these complications. Fluoroquinolones are valued agents in treating several infections (**TABLE 1**),[1–4] and this article makes clinical recommendations, based on published evidence, to help you decrease the risk of dysglycemia.

Scope of the problem

The most recent article published on this subject identified 178 episodes of dysglycemia requiring hospitalization within 30 days of treatment—this following 16,697 outpatient courses of gatifloxacin, for a rate of 1.1%. Compared with gatifloxacin, rates were substantially lower for ciprofloxacin (0.3%), levofloxacin (0.3%), and moxifloxacin (0.2%) and for comparison antibiotics (those not associated with glucose metabolism problems), such as second-generation cephalosporins (0.2%) and macrolides (0.1%).[5]

However, an earlier analysis of inpatients receiving gatifloxacin, levofloxacin, or ciprofloxacin reported similar dysglycemia rates of 1.01%, 0.93%, and 0%, respectively.[6] Postmarketing

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CORRESPONDENCE
Martin Catero, MD
Heuser Family Medicine Center, 7301 East Second Street, Suite 210, Scottsdale, AZ 85251.
mcatero@shc.org

TABLE 1

FDA-approved indications for 4 fluoroquinolones

Introduced in the 1980s, fluoroquinolones boast excellent oral absorption and bioavailability. They have revolutionized the treatment of several bacterial infections, including community-acquired pneumonia and disorders of the genitourinary tract. Each new generation of fluoroquinolone has expanded the spectrum of gram positive, atypical, and anaerobic bacterial coverage, while minimizing side effects.

	GATIFLOXACIN	LEVOFLOXACIN	MOXIFLOXACIN	CIPROFLOXACIN
Urinary tract infections		✓		✓
Acute pyelonephritis	✓	✓		✓ (children)
Chronic bacterial prostatitis		✓		✓
Acute bacterial exacerbation of chronic bronchitis		✓	✓	✓
Community-acquired pneumonia	✓	✓	✓	✓ (except *S pneumo*)
Nosocomial pneumonia		✓		
Acute sinusitis	✓	✓	✓	✓
Skin and skin structure infections	✓	✓		✓
Bone and joint infections				✓
Complicated intra-abdominal infections				✓
Infectious diarrhea				✓
Gonorrhea	✓			✓
Inhalational anthrax				✓

Source: Bristol-Myers Squibb 2006;[1] Bayer 2004;[2] Ortho-McNeil 2004;[3] Bayer 2003.[4]

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Hypoglycemia may also be caused by a drug-drug interaction

surveillance studies further confirm these rates.[7]

The 2 North American governmental drug regulatory agencies report the following.

Health Canada: Twenty-eight cases of gatifloxacin-associated dysglycemia, with 2 deaths, over a 2-year period—89% of affected patients had preexisting diabetes mellitus and 67% of dysglycemia cases were hypoglycemic events.[8]

US Food and Drug Administration: Fifty-six times as many reports of dysglycemia filed for gatifloxacin than for other fluoroquinolones; its data revealed rates of hypoglycemia ranging from 0.65% to 2%.[9]

Hypoglycemia: Exact cause uncertain

Sulfonylurea-like action. The most plausible mechanism is a sulfonylurea-like action on pancreatic beta cells, thus increasing insulin secretion.[10] Drugs such as quinine and mefloquine share chemical structures with fluoroquinolones and work in a similar manner to release insulin.[11,12] Individual fluoroquinolones differ greatly in their affinity for pancreatic beta cells. Gatifloxacin and temafloxacin have greater affinity, and thus greater hypoglycemic effect than other fluoroquinolones such as ciprofloxacin and levofloxacin.[12]

Drug-drug interaction. Hypoglycemia may also be caused by a drug-drug interaction. Glyburide levels have been

reported to increase in patients with hepatic or renal impairment taking ciprofloxacin.[13] Gatifloxacin has been shown to augment the activity of several oral hypoglycemics, namely repaglinide, glyburide, pioglitazone, and glimepiride.[14] Similar effects have been documented between glyburide and levofloxacin, moxifloxacin, and ciprofloxacin.[10]

P450 isoenzyme interaction may also be a factor in fluoroquinolone-associated dysglycemia.[16] This explanation is the least plausible given that, although hypoglycemia may be seen with all fluoroquinolones, ciprofloxacin is the only one with any appreciable hepatic P450 metabolism.

Frequency of hypoglycemic events

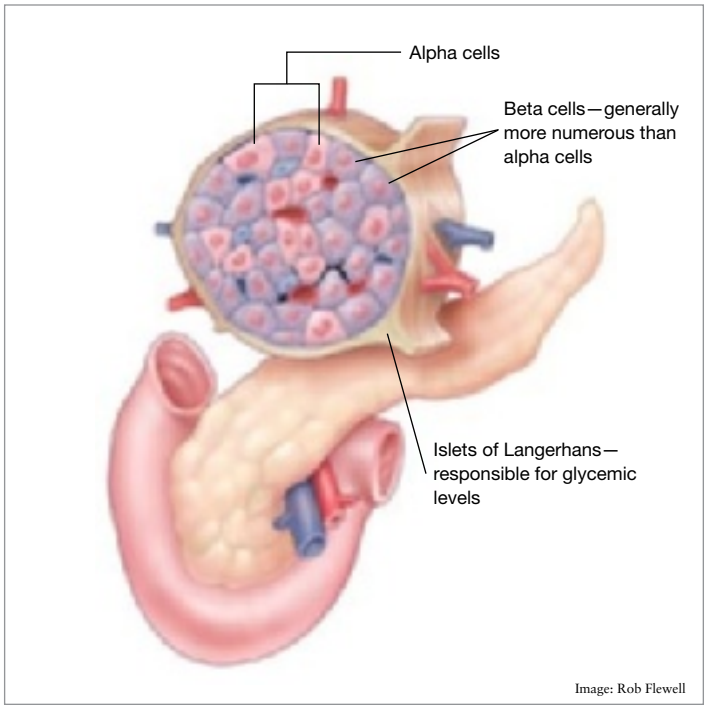
Clinical studies regarding the effect of fluoroquinolones on glucose homeostasis are difficult to interpret because they have yielded conflicting results. Differences in patient demographics, concomitant medications, existing medical conditions, and even the definitions of hypo- and hyperglycemia used may account for the varying results. The following is a synopsis of the available literature on fluoroquinolone-associated hypoglycemia. Only randomized controlled trials, case-control studies, and chart reviews are included.

Studies finding a hypoglycemic effect. The most comprehensive report on fluoroquinolone-associated dysglycemia screened the medical records of more than 1.4 million elderly patients from 2002 to 2004. During this case-control study, 788 patients were evaluated in an emergency department or admitted to a hospital for treatment of hypoglycemia within 30 days of receiving a fluoroquinolone, macrolide, or second-generation cephalosporin antibiotic. Ninety-two percent of patients suffering hypoglycemia were also being treated for diabetes. Gatifloxacin had the highest rate of hypoglycemic events, with an adjusted odds ratio of 4.3 vs a macrolide. Levofloxacin was also associated with a higher rate of hypoglycemia, with an adjusted odds ratio of 1.5. No increased risk was reported for moxifloxacin, ciprofloxacin, or second-generation cephalosporins.[5]

Additional compelling evidence for a hypoglycemic effect comes from a case-control study spanning 2 years and involving 7287 patients who received gatifloxacin or levofloxacin. One-hundred thirteen patients (1.6%) recorded a glucose level <51 mg/dL. Median time from start of treatment to onset of hypoglycemia was 1 day. The number needed to harm for gatifloxacin compared with levofloxacin to have 1 additional hypoglycemic event was 101. Concomitant hypoglycemic drug treatment, renal failure, and sepsis syndrome were the top associated risk factors, and significantly predicted hypoglycemia within 96 hours.[16]

FIGURE

Fluoroquinolones differ greatly in their affinity for pancreatic beta cells



As with hypoglycemia, most cases of fluoroquinolone-associated hyperglycemia have occurred in patients with non-insulin-dependent diabetes mellitus and mild-to-moderate renal insufficiency.

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Gatifloxacin has been shown to augment the activity of repaglinide, glyburide, pioglitazone, and glimepiride

Image: Rob Flewell

TABLE 2

Studies that found no dysglycemic effects of fluoroquinolones

STUDY DESIGN	NO. OF PATIENTS	RESULTS/CONCLUSIONS
Randomized, double-blind, placebo-controlled trial of patients with NIDDM treated gatifloxacin[17]	48	Glucose levels not significantly different in patients treated with gatifloxacin or ciprofloxacin compared to placebo.
Randomized, double-blind, placebo-controlled trial in healthy males receiving variable doses of gatifloxacin[18]	40	Mean change in oral glucose tolerance test, glucose, insulin, and C-peptide levels comparable among gatifloxacin and placebo treatment groups.
Pooled analysis of 32 (30 controlled) phase II/III studies of moxifloxacin[19]	8474 test patients and 6257 control patients	No drug-related hypoglycemic events among patients treated with moxifloxacin. Seven (<0.1%) cases of moxifloxacin-associated hyperglycemia.
Pooled data from five postmarketing studies of moxifloxacin[19]	46,130 patients	No episodes of drug-related hypo- or hyperglycemia among patients treated with moxifloxacin.
Analysis of four clinical trials (including 2 randomized controlled trials) of gatifloxacin treatment for recurrent acute otitis media or acute otitis media treatment failure[20]	867 children ages 6 months to 7 years	No evidence of alteration of glucose homeostasis during treatment and up to 1-year follow-up

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Hypoglycemic events typically occur within the first 3 days of treatment

Studies finding no hypoglycemic effect. One of the first important studies evaluated 48 patients, ages 18 to 45, with non-insulin-dependent diabetes mellitus (NIDDM) controlled with diet and exercise. In this randomized, double-blind, placebo-controlled study, gatifloxacin had no significant effect on glucose tolerance or pancreatic beta cell function. Though gatifloxacin caused brief increases in serum insulin levels, and though fasting glucose levels up to 6 hours after gatifloxacin administration showed a downward trend through the first 10 days of treatment, the differences in glucose levels were not significantly different when compared with placebo. Similar results were found for ciprofloxacin.[17]

A second randomized, double-blind, placebo-controlled trial was performed using 40 healthy (non-diabetic) men randomized to receive variable doses of gatifloxacin. Mean change in oral glucose tolerance test and in fasting serum glucose, insulin, and c-peptide concentrations were comparable among gatifloxacin and placebo treatment groups. Mild transient decreased serum glucose levels were noted at the completion of a one-hour infusion of gatifloxacin.[18] These 2 studies and others finding no hypoglycemic effect are listed in **TABLE 2**.[17–20]

Take-home points

In the case-control studies finding an effect, most instances of fluoroquinolone-associated hypoglycemia occurred in patients with NIDDM and mild-to-moderate renal insufficiency. Many affected patients were taking oral hypoglycemics and at doses in excess of manufacturers' recommendations.[21] Hypoglycemic events typically occurred within the first 3 days of treatment, but could occur after a single dose.

Hyperglycemia: Mechanism is poorly understood

In contrast to the hypoglycemic effects of fluoroquinolones, the mechanism of fluoroquinolone-associated hyperglycemia is poorly understood. While the package insert for gatifloxacin says the drug may decrease insulin secretory granules in pancreatic beta cells, package inserts for the other common fluoroquinolones make no mention of this

mechanism.[1–4] A 1993 report on 10 patients found that hyperglycemic events were likely secondary to fluoroquinolone overdosage or a toxic effect of the drug in patients with concomitant renal insufficiency.[22]

But hyperglycemia occurs more often than hypoglycemia

While data from case reports and postmarketing analyses describe a higher frequency of fluoroquinolone-associated hyperglycemia than hypoglycemia, there is much less evidence upon which to provide specific practice recommendations.

Studies finding a hyperglycemic effect. Cited previously, the case-control study screening medical records of 1.4 million elderly patients reported 470 patients evaluated in an emergency department or hospital for hyperglycemia within 30 days after receiving a fluoroquinolone, macrolide, or second-generation cephalosporin. Once again, gatifloxacin was shown to have the highest risk with an adjusted odds ratio of 16.9 vs a macrolide. No increased risk was detected for levofloxacin, moxifloxacin, or ciprofloxacin.[5]

A retrospective chart review of more than 17,000 hospitalized patients receiving levofloxacin, gatifloxacin, or ceftriaxone, showed 101 patients with glucose concentrations >200 mg/dL or <50 mg/dL within 72 hours of receiving the drugs. Of these 101 patients, 92 experienced hyperglycemia. Most of these patients had underlying renal insufficiency. Eighty-nine percent had diabetes mellitus and 40% were taking oral hypoglycemics. Hyperglycemia rates were greater with levofloxacin and gatifloxacin than with ceftriaxone; no difference was found between levofloxacin and gatifloxacin.[6]

Finally, a second retrospective chart review of a VA population identified 64,076 prescriptions written for fluoroquinolones between 1998 and 2003. More than 10,000 glucose values were measured during treatment or within 7 days of treatment completion. Hyperglycemia occurred much more often than hypoglycemia—in 11.6% of 32,000 patients. The majority (59%) of hyperglycemic episodes occurred in diabetic patients, and it was not clear that fluoroquinolone use caused the hyperglycemia. In contrast to the data listed above, gatifloxacin had a lower rate of associated hyperglycemia than either levofloxacin or ciprofloxacin.[23]

Studies finding no hyperglycemic effect. The studies reviewed in the section on hypoglycemia found no clinically significant hyperglycemic effect of fluoroquinolones.

Take-home points

As with hypoglycemia, most cases of fluoroquinolone-associated hyperglycemia have occurred in patients with NIDDM and mild-to-moderate renal insufficiency. More definitive risk factors for hyperglycemia include decreased insulin secretion (eg, IDDM), decreased insulin sensitivity

Methods

We searched PubMed for literature published on fluoroquinolone-associated dysglycemia between March 1966 and March 2006. We used the following search terms: "fluoroquinolones and hypoglycemia," "fluoroquinolones and hyperglycemia," "fluoroquinolones and glucose homeostasis," "fluoroquinolones and glucose control," and "fluoroquinolones and dysglycemia." These 5 searches returned a total of 37 articles.

Most of the articles were case reports and pharmacologic reviews, and these were not considered in our analysis. Eleven original studies remained. We eliminated 3 of these studies: one tracked insulin levels in 12 patients with non-alcoholic steatohepatitis treated with a fluoroquinolone; a second study evaluated gatifloxacin pharmacokinetics; a third one focused on the mechanism, rather than the frequency, of fluoroquinolone-associated dysglycemia. We assessed the remaining 8 studies for quality, and the Strength of Recommendation Taxonomy (SORT) was applied to provide specific practice recommendations.

For more information on SORT, see "Strength of recommendation taxonomy (SORT): A patient-centered approach to grading evidence in the medical literature," in the February 2004 *Journal of Family Practice* (pages 111–120).

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Most cases of hyperglycemia occur in patients with NIDDM and mild-to-moderate renal insufficiency

(eg, NIDDM), advanced age, high carbohydrate intake, acute infection, stress, and corticosteroid use.[24] While an association with fluoroquinolone use appears to be multifactorial and dependent on these underlying host factors, strong evidence is lacking.[11] As opposed to the timing of hypoglycemic events, review of several case reports revealed that fluoroquinolone-associated hyperglycemia has generally occurred later in treatment, usually after 4 days of therapy, and with higher doses.

Summary of practice recommendations

The following conclusions and recommendations can be made based on the studies reviewed.

First, because the rate of fluoroquinolone-associated dysglycemia is highest with gatifloxacin, and most patients who experience fluoroquinolone-associated dysglycemia have diabetes, gatifloxacin should be avoided in patients who have diabetes (SOR: A).

Second, it's wise to not use any fluoroquinolone in elderly patients with diabetes mellitus (especially those taking sulfonylureas), hepatic insufficiency, and/or renal insufficiency (SOR: A). If a fluoroquinolone must be used in these patients, favor levofloxacin or moxifloxacin over gatifloxacin (SOR: B).

Third, discontinue fluoroquinolone therapy if a patient experiences symptoms of hypo- or hyperglycemia and/or blood glucose levels fall below 60 mg/dL or rise above 200 mg/dL (SOR: C). If symptomatic hypo- or hyperglycemia does occur, administer appropriate therapy, and if necessary, admit the patient to the hospital for appropriate treatment (SOR: C). ■

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Avoid gatifloxacin for patients who have diabetes

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