Hypoglycemia and Hyperglycemia Associated with Gatifloxacin Use in Elderly Patients

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Fourth-generation quinolones, such as levofloxacin (Levofloxin) and gatifloxacin (Tequin), have become widely used in outpatient and inpatient settings. These quinolones add Gram-positive bacterial coverage and maintain the Gram-negative coverage of earlier quinolones. This broad-spectrum coverage has numerous clinical applications, such as respiratory, gastrointestinal, or urinary systems infections. Because quinolones are equally bioavailable orally or intravenously, they are often used for patients at higher risk for serious infection in either outpatient or hospital settings.[1]

Gatifloxacin may possess some advantages over other quinolones. In vitro, gatifloxacin is 2 to 4 times more active against *Streptococcus pneumoniae* than levofloxacin.[2] It also possesses activity against *Staphylococcus aureus*, some Enterococci, and atypical pathogens, such as *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*.[2] In our community hospital with 250 beds, it is the quinolone of choice.

Within 2 months in our institution, however, 4 cases of hypoglycemia or hyperglycemia occurred in patients treated with gatifloxacin that either caused hospitalization or lengthened the patients' hospital stay. A literature search revealed no discussion about the potential severity of the hypo/hyperglycemic side effect; thus, we briefly present these cases.

Case Reports

Case 1

An 82-year-old man hospitalized for digoxin toxicity had stable serum glucoses on his glipizide (Glucotrol) 5 mg daily. In the hospital, he developed fever. The patient was allergic to penicillin and was started on gatifloxacin (Tequin) based on the empirical evidence. He received 400 mg of gatifloxacin orally and 5 mg of glipizide at 9:00 AM. At noon, his capillary blood glucose was 260 mg/dL, and he received 3 units of regular insulin. By 5:00 PM, he was noted to be confused, with a serum glucose of 50 mg/dL. His hypoglycemia persisted despite intravenous glucose (100 g/L) for 12 hours. The patient was eating, and eventually his serum glucose returned to the normal range. The following morning, he again received gatifloxacin and glipizide. By 4:00 PM, he had symptomatic hypoglycemia with a serum glucose of 60 mg/dL. The gatifloxacin and glipizide were discontinued, and the patient's serum glucose increased to the 200 mg/dL level within 24 hours. The glipizide was restarted at 2.5 mg/day, and the patient's serum glucose remained stable until discharge.

Case 2

A 68-year-old woman with diabetes taking 1.25 mg/day of glyburide (Micronase) was hospitalized for a congestive heart failure exacerbation. Her urinalysis suggested a urinary tract infection, and the patient began receiving 200 mg/day of oral gatifloxacin. Within 24 hours, the patient developed hypoglycemia. Her capillary blood glucose was between 70 and 80 mg/dL for 2 days despite intravenous glucose and discontinuation of her glyburide. The gatifloxacin was discontinued on the fifth hospital day, and the patient's blood glucose increased to above 200 mg/dL. The glyburide was restarted and the blood glucose levels remained in the 150 to 200 mg/dL range.

Case 3

An 82-year-old woman with coronary artery disease and non–insulin-dependent diabetes mellitus who was taking 1000 mg of metformin (Glucophage) twice a day and 10 mg of glipizide (Glucotrol

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XL) daily had an uneventful hospitalization for pneumonia and was discharged from the hospital on 200 mg/day of gatifloxacin. Within 48 hours, the patient returned to her physician because she "didn't feel well." Her serum glucose was over 500 mg/dL. After hospitalization, her serum glucose level rapidly declined on a low-dose insulin drip. On the following day, however, when she was receiving subcutaneous insulin, her blood glucose again increased to more than 400 mg/dL. She had received an oral dose of gatifloxacin that morning. The gatifloxacin was discontinued, and she had no further episodes of severe hyperglycemia.

Case 4

A 91-year-old woman with chronic obstructive pulmonary disease (COPD) but no history of hyperglycemia or diabetes experienced an exacerbation of her COPD. She was given a prescription for oral prednisone and gatifloxacin. Within 48 hours, she was admitted to the hospital for nonketotic hyperglycemia, with a serum glucose level of more than 1000 mg/dL. She had been on prednisone previously and had experienced no episodes of hyperglycemia.

Discussion

In most cases, quinolones are well tolerated. Rarely, however, quinolones can have severe adverse effects, such as potentially fatal ventricular arrhythmias from prolongation of the QT interval, or significant drug interactions, such as with digoxin or warfarin.[1] A review article warns that quinolones "may cause hypoglycemia and/or hyperglycemia if used concomitantly with antidiabetic agents."[1] The clinician may be unaware of the need to adjust an oral hypoglycemic medication, such as glyburide or glipizide that is being taken concurrently with gatifloxacin, especially because some initial literature on gatifloxacin stated "gatifloxacin can be administered with glyburide without an apparent risk of pharmacokinetic or pharmacodynamic interaction. "[3]

Side-effect data for gatifloxacin available from clinical efficacy studies show the most commonly reported events were nausea (8%), vaginitis (6%), diarrhea (4%), and headache (3%).[4] Hypoglycemia was noted as rare (<0.1%), and hyperglycemia was not mentioned in the original package insert.[5] Small studies examined gatifloxacin's effect on glucose metabolism. A randomized controlled trial with 48 men and women with diabetes controlled with diet and exercise was designed to compare the effects of oral gatifloxacin versus ciprofloxacin versus placebo on glucose metabolism. Measurements of serum glucose and serum insulin levels were drawn daily after fasting and after 75-mg oral glucose tolerance tests. An increase in insulin levels compared with placebo was shown after the first dose of 400 mg of gatifloxacin but was only statistically significant for a short-term effect. By day 10, the long-term effect on insulin levels was determined to be not statistically significant. Because no patient showed any sign or symptom of hypoglycemia, the effect was determined to be not clinically significant as well.[6] A pharmacokinetic study of 40 men without diabetes monitored serum glucose and insulin levels after 200 and 400 mg of gatifloxacin was administered intravenously. After infusion, a "transient, mild to moderate *decrease* in fasting serum glucose" was noted for both doses. However, no corresponding elevated insulin level was noted, and the study concluded this effect was not clinically significant.[7] Conversely, in another study, patients with type 2 diabetes who were taking glyburide were given 400 mg of gatifloxacin daily for 10 days; they showed a small *increase* in fasting glucose by day 4, but it was not statistically significant.[8]

At doses of 200 to 800 mg, gatifloxacin's pharmacokinetics are "linear, time-independent and predictable," with the caveat "as evaluated in 40 healthy adult males."[7] Eighty percent of the gatifloxacin is excreted in the urine unchanged, with a half-life of 7 to 14 hours.[8] It is recommended that the dose of gatifloxacin be reduced by 50% in patients with creatinine clearance levels of <40 or 50 mL/min.[7,8] In general, the patients in the gatifloxacin studies were significantly younger and healthier than the hospitalized patients in our cases. Because of a loss in muscle mass in elderly patients, serum creatinine levels may not be an accurate assessment of renal function. Creatinine clearance is a more accurate estimate of renal function than serum creatinine.[9] The patients in our cases had renal insufficiency, with their serum creatinine levels in the 1.5 to 1.8 mg/dL range. Their estimated creatinine clearances for their ages were well below 40 mL/min. Only 2 of the patients received gatifloxacin at a reduced dosage of 200 mg/day. Perhaps the 400-mg dose of gatifloxacin in these el-

derly patients with renal insufficiency exaggerated the effect of gatifloxacin, causing hypoglycemia or hyperglycemia. In addition, the severely ill patients could have had a rapid decrease in their renal function, increasing the serum concentration of gatifloxacin. In patient 2, glyburide was discontinued before the she began to receive gatifloxacin; however, serum glucose remained unstable until the gatifloxacin was discontinued as well. Thus, the hypoglycemic effect of gatifloxacin seemed to occur also in the absence of the oral hypoglycemic drug. As for hyperglycemia, it is possible that the small increase in fasting glucose in younger volunteers taking glyburide will translate to a much greater increase in serum glucose in elderly persons. In the fourth case, the prednisone possibly promoted this effect and produced significant hyperglycemia. Our cases implicate gatifloxacin as contributing to both hypoglycemia and hyperglycemia in elderly patients.

Conclusions

As the "baby-boomer" population of the United States becomes older and people take more medications for long-term medical conditions, the clinician will need to have more awareness of drug interactions and of the route of excretion of drugs. As these cases involving gatifloxacin suggest, a drug found to be "safe" in clinical trials with younger adults might have very significant deleterious medical effects in elderly or ill patients. Clinicians often remember to adjust medications for patients with significant renal insufficiency or failure, but fail to remember that a creatinine of 1.5 mg/dL in an 80-year-old, 115-pound woman can indicate an estimated creatinine clearance of 25 mL/min. Even at the recommended 50% decrease of gatifloxacin for renal insufficiency, the cases above may indicate an augmentation of the effect of gatifloxacin on glucose metabolism. For gatifloxacin and oral hypoglycemic medications, the interaction between the 2 medications may be more significant than previously realized. During the postmarketing period, reports to the manufacturer of gatifloxacin (Tequin) of hypoglycemia and hyperglycemia caused a revision of the package insert to include warnings of serious disturbances in glucose metabolism.[4] Clinicians should have a heightened awareness of the potential for hypoglycemic and hyperglycemic effects among their elderly patients with renal insufficiency or with their diabetic patients when prescribing gatifloxacin.

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