Gatifloxacin-Associated Corrected QT Interval Prolongation, Torsades de Pointes, and Ventricular Fibrillation in Patients with Known Risk Factors

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Drugs not commonly considered to be cardioactive agents have been reported to cause prolongation of the corrected QT interval with resultant torsades de pointes or ventricular fibrillation. We report 4 cases of gatifloxacin-associated cardiac toxicity in patients with known risk factors for this adverse event.

Drug-acquired corrected QT (QTc) interval prolongation is increasingly being recognized as an adverse event. Although cardiovascular drugs, such as the class Ia and III antiarrhythmics, are known to prolong the QTc interval, other noncardiovascular drugs have been reported to prolong the QTc interval [1]. Fluoroquinolones as a class have been associated with QTc interval prolongation [2–4]; newer fluoroquinolones now have warnings on their product labels to avoid use of these drugs in patients with preexisting prolonged QTc interval or in those receiving agents concurrently known to prolong the QTc interval [5–7]. Prolongation of the QTc interval can lead to the development of torsades de pointes (TdP), which can result in ventricular fibrillation [1]. We report 4 cases of gatifloxacin-associated TdP or ventricular fibrillation in patients considered at high risk for drug-acquired QTc interval prolongation.

**Case 1.** An 81-year-old woman developed *Staphylococcus aureus* bacteremia secondary to an intravenous catheter–related infection. She was treated with ceftriaxone for 2 weeks and discharged from the hospital, to continue gatifloxacin therapy. The patient’s medical conditions included congestive heart failure, hypertension, atrial fibrillation, anemia, type II diabetes mellitus, and chronic renal insufficiency (serum creatinine level, 3.3 mg/dL). At the time of discharge, her cardiac status was stable, and her QTc interval was 448 ms. Medications she was receiving at the time of discharge included gatifloxacin (400 mg orally daily), amiodarone (200 mg daily), isosorbide mononitrate (60 mg daily), extended-release potassium (40 mEq daily), gluburide (2.5 mg daily), omeprazole (20 mg daily), and bumetanide (2 mg twice per day).

The patient received 3 doses of gatifloxacin and was readmitted to the hospital after 2 episodes of syncope. An electrocardiogram (ECG) performed at admission revealed QTc interval prolongation (520 ms) and TdP. Laboratory values were normal, except for a serum creatinine level of 3.3 mg/dL and a magnesium level of 3.5 mg/dL. The patient was admitted to the cardiac intensive care unit for stabilization and monitoring. Amiodarone and gatifloxacin were discontinued. Her cardiac status stabilized, and, the next day, amiodarone was reintroduced. ECGs obtained during the ensuing 10 days showed that the QTc interval decreased from 499 ms to 431 ms, and the bradycardia developed, for which a pacemaker was implanted. After reintroduction of amiodarone at the previous dosage, no further episodes of TdP were noted.

**Case 2.** A 60-year-old white woman was admitted to the hospital for syncope. She reported having weakness for 3 days prior to admission and had symptoms of an upper respiratory infection without fever, rigors, or productive cough. Her medical history included coronary artery disease that had required placement of a stent in the right coronary artery 2 years previously, hypertension, rheumatoid arthritis, insulin-dependent type II diabetes mellitus, hypothyroidism, and depression. The medications she was currently taking were aspirin (325 mg daily), prednisone (7.5 mg daily), amitriptyline (20 mg daily), insulin, valsartan (160 mg daily), lansoprazole (15 mg daily), pravastatin (40 mg daily), thyroid hormone (0.15 µg daily), folic acid (2 mg daily), and rofecoxib (25 mg daily), hydrocodone bitartrate and acetaminophen (7.5 and 500 mg, respectively, as needed), and methotrexate (10 mg weekly).

The patient was given 1 dose of gatifloxacin (400 mg orally) and, 2 h later, had a 2-min episode of syncope. On examination, her heart rate was 40 beats/min, and an ECG revealed third-degree heart block and a QTc interval of 500 ms. Her cardiac...
monitor showed episodes of TdP. Laboratory values were within the normal range; the serum creatinine level was 0.8 mg/dL.

The patient had a permanent cardiac pacemaker implanted, and no further doses of gatifloxacin were administered. Twenty-four hours after discontinuation of the gatifloxacin, her QTc interval was 450 ms, and no further episodes of TdP occurred even when the pacemaker was inactivated and the heart rhythm monitored.

Case 3. A 74-year-old man with a history of congestive heart failure was admitted to the hospital for severe antibiotic-associated pseudomembranous colitis. The medications he was currently taking were metoprolol (5 mg every 6 h), enalapril (2.5 mg twice per day), furosemide (80 mg daily), omeprazole (20 mg daily), vancomycin (500 mg every 6 h), and magnesium oxide (400 mg 3 times per day).

During hospitalization, the patient developed worsening signs of congestive heart failure. A transthoracic echocardiogram revealed decreased left ventricular function with anterior and anteroseptal regional wall–motion abnormalities. His ECG revealed a heart rate of 110 beats/min and multifocal atrial tachycardia with a QTc interval of 443 ms. A pneumonic process superimposed on congestive heart failure was suspected, and the patient was treated with gatifloxacin (400 mg iv every 24 h). Two hours after receiving the first dose of gatifloxacin, his QTc interval had increased to 512 ms. Two days later, he received a third dose of gatifloxacin, and, 90 min later, he developed sustained TdP (as noted on a cardiac monitor) and had cardiopulmonary arrest, which was witnessed by a clinician. Laboratory studies performed the morning of the event revealed a serum potassium level of 3.1 mEq/L, a magnesium level of 1.9 mg/dL, and a creatinine level of 1.3 mg/dL.

The patient was resuscitated but, during the next several days, failed to regain cognitive function and died of hypoxia sustained during the cardiac arrest. Post-mortem examination revealed senile-type cardiac amyloidosis and 3-vessel coronary artery disease with evidence of acute ischemic changes.

Case 4. A 65-year-old white man presented to his physician with a productive cough. His medical history was significant for hypertension, depression, chronic bronchitis, hiatal hernia, and atrial flutter. The medications he was currently taking were imipramine (100 mg daily), amiodarone (200 mg daily), felodipine (2.5 mg daily), doxazosin (8 mg daily), and hydrochlorothiazide/triamterine (25/37.5 mg daily). The patient had documented QTc intervals of 480–530 ms while receiving paroxetine (20 mg daily) or phenelzine (30 mg daily) 2 years prior to the reported physician visit and 454 ms 2 weeks before the visit to his physician. He was given 400-mg gatifloxacin tablets (as samples) and instructed to take 1 tablet daily. The patient took 1 dose of gatifloxacin at home and later (time after dose, unknown) was found collapsed on the floor and unresponsive. Emergency medical technicians were called and arrived within 10 min. The patient was noted to have ventricular fibrillation, a potential sequela of drug-acquired QTc interval prolongation, and TdP. Resuscitation was unsuccessful. At autopsy, no evidence of significant coronary artery disease was found. The serum creatinine level at autopsy was 2.5 mg/dL, the serum amiodarone concentration was 2.7 μg/mL, and the imipramine concentration was 0.14 μg/mL (none of these values are elevated). No evidence of drugs of abuse was detected in a urine sample.

Discussion. A variety of drugs are reported to prolong the QTc interval [1]. The presumed mechanism of drug-acquired QTc interval prolongation is blockade of the HERG (human ether a go-go) potassium channel [8].

Quinolone antibiotics have been associated with prolongation of the QTc interval. In vitro studies have suggested that sparfloxacin, grepafloxacin, moxifloxacin, and gatifloxacin exhibit the greatest blockade of the HERG potassium channel and that levofloxacin, ciprofloxacin, and ofloxacin require the highest concentrations to produce HERG potassium channel blockade [9]. Drugs such as sparfloxacin and grepafloxacin have been removed from the market in the United States, in part because of their potential for QTc interval prolongation. The QTc interval appears to be the clinical marker of highest utility for prediction of TdP [1, 11]. There have been 3 published cases of TdP associated with treatment with gatifloxacin [10, 11], 2 cases associated with levofloxacin [3, 12], 1 associated with moxifloxacin [13], and 0 associated with ciprofloxacin [7]. Although it is difficult to know the exact number of treatment courses administered for each of these agents, the number of levofloxacin and ciprofloxacin treatment courses greatly exceeds that of gatifloxacin and moxifloxacin (the newer agents), and, thus, at this time, the risks associated the newer agents appear to be lower but, in fact, may not be lower.

Risk factors for drug-acquired QTc interval prolongation appear to be female sex, presence of underlying cardiac disease (including congestive heart failure), advanced age, hypokalemia, hypomagnesemia, and use of concomitant drugs that are known to prolong the QTc interval (e.g., class Ia and III antiarrhythmic agents) [1, 11, 14]. Limited data in humans have implicated a dose-effect relationship for drugs that prolong the QTc interval; thus, one would anticipate that any factor that would increase drug exposure (i.e., drug interactions or renal disease) might increase the risk of QTc interval prolongation. Of our patients, 2 were women, 3 were receiving drugs known to prolong the QTc interval (amiodarone, imipramine, and amitriptyline), all had a history of heart disease (1 patient with documented QTc interval prolongation at baseline before receiving any additional drugs that prolong the QTc interval and 2 patients with congestive heart failure), and 3 had mildly to moderately elevated serum creatinine (these patients were receiving doses of gatifloxacin not adjusted for renal impairment).
The patients receiving amiodarone had a normal or nearly normal QTc interval before or after the introduction or cessation of gatifloxacin therapy and no previous episodes of TdP while receiving amiodarone alone.

Our reports of gatifloxacin-associated TdP and ventricular fibrillation should alert clinicians to the potential for this serious adverse effect in patients who are treated with noncardiac drugs. Quinolones are administered to a substantial number of patients to treat respiratory and urinary tract infections. Many of these patients may have ≥1 risk factor for prolonged QTc interval; when known risk factors exist, drugs should be selected with caution. In these patients, drugs not known to induce QTc interval prolongation or drugs associated with a lower incidence of this adverse effect should be considered. A thorough listing of drugs that can prolong the QTc interval is available online at http://www.qtdrugs.org.

References