

## Case Report

# Advancing Age and Renal Impairment as Important Predisposing Factors of Gatifloxacin-Induced Hyperglycemia in Non-Diabetes Patients

Mudjalín Ovartlarnporn MD\*,  
Wallaya Jongjaroenprasert MD\*

\* Endocrine Unit, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University

There have been case reports about adverse effects to glucose homeostasis related to gatifloxacin use. The authors report an elderly, non-diabetic patient who developed severe hyperglycemia after receiving oral gatifloxacin 400mg/d. He was a 73-year-old male, patient with a history of hypertension, cured vesical pheochromocytoma, idiopathic dilated cardiomyopathy, chronic renal insufficiency (baseline serum creatinine of 1.7 mg/dL), and gouty arthritis admitted to the hospital with a diagnosis of acute bronchitis. Seven days after initiating gatifloxacin, his symptoms were improved. Subsequently he developed polyuria, polydipsia, and fatigue with an increase in serum creatinine to 2.8 mg/dL, and random plasma glucose levels elevated to 903 mg/dL. Gatifloxacin was stopped. Intravenous regular insulin infusion was administered. Euglycemia was achieved within 8 hours after fluid rehydration and only low dose insulin was required. He maintained normal glucose levels without any antidiabetic drugs afterward. Old age and renal impairment were considered significant contributing factors for this hyperglycemic adverse event from gatifloxacin.

**Keywords:** Gatifloxacin, Hyperglycemia, Fluoroquinolone, Glucose

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The new fluoroquinolones, with the special property of broad spectrum of antimicrobial coverage, relatively benign adverse effect profiles, and once-daily dosing, are experiencing a vast degree of use in both hospitals and outpatient clinics. However, with this increased utilization also come reports of previously uncommon adverse events, in particular, the effects on glucose homeostasis. The exact mechanism of this adverse effect is still unknown. The authors report here a patient who developed severe hyperglycemia following administration of oral gatifloxacin 400 mg daily for his acute bronchitis.

### Case Report

A 73-year-old Thai man presented with low-grade fever, with some productive cough and non-

massive hemoptysis. He was then admitted with a diagnosis of acute bronchitis. The patient's medical history was significant for hypertension, cured primary vesical pheochromocytoma, idiopathic dilated cardiomyopathy with biventricular implantable cardioverter defibrillator therapy for his sustained ventricular tachycardia, chronic renal insufficiency with baseline serum creatinine 1.7 mg/dL, and intercritical gouty arthritis. His fasting plasma glucose levels had been checked on a regular basis, and the result at 2 months prior to admission was 4.6 mmol/L (83 mg/dL). His current medications included amiodarone 200 mg/day, hydrochlorothiazide 25 mg/day, enalapril 5 mg/day, finasteride 5 mg/day, digoxin 0.25 mg trice a week, carvedilol 1.55 mg/day, warfarin 0.75 mg/day, torasemide 10 mg/day, and halcion 0.25 mg/day. His chest examination was normal. Chest film performed on admission revealed no pulmonary infiltration.

On admission, his basic metabolic profiles showed sodium 134 mEq/L (normal 136-145), potas-

Correspondence to : Jongjaroenprasert W, Endocrine Unit, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Rama 6 Rd, Rajathevi, Bangkok 10400, Thailand. Phone: 0-2201-1647, E-mail: rawjj@mahidol.ac.th

sium 3.34 mEq/L (3.5-5.1), chloride 95 mEq/L (98-107), carbon dioxide 26.5 mEq /L (22.0-29.0), blood urea nitrogen (BUN) 45 mg/dL (8-22), serum creatinine 1.8 mg/dL (0.6-1.3), fasting plasma glucose 97 mg/dL (70-110), and calcium 8.6 mg/dL (8.9-10.3). Also of note, was a white blood cell count of  $15.8 \times 10^3/\text{mm}^3$  (4.8-10.8). Four hundred milligrams of oral gatifloxacin was prescribed with his regular medications.

Five days after antibiotic administration, the patient gradually experienced fatigue, polyuria, and polydipsia. Three days later, the clinical features of moderate dehydration were observed. His plasma glucose was examined and the levels of 903 mg/dL were detected. Calculated effective serum osmolality was 316 mmol/L and ketone bodies were not found in both urine and serum by nitropusside test. Serum creatinine rose to 2.8 mg/dL. Severe hyperglycemia with impending hyperosmolar hyperglycemic crisis was diagnosed. The patient was then moved to critical care unit and intensive intravenous regular insulin infusion was administered. Normal glycemia was achieved within 8 hours after intravenous fluid and only low dose insulin was required.

After a careful medications review, the authors were not able to demonstrate any obvious precipitating factors leading to his hyperglycemic state except 7 days of gatifloxacin administration. His bronchitis significantly improved before developing hyperglycemia. His antimicrobial agent was discontinued and capillary blood glucose was monitored everyday before each meal. The authors found that his glycemic state returned to normal easily thereafter without prescribing any insulin or oral glucose lowering agents (fasting plasma glucose < 100 mg/dl and random glucose < 140 mg/dl). Glycosylated hemoglobin (HbA1c) was checked and it was 7.4% 2 days after the events and decreased to 6.3% at one month later.

## Discussion

The authors reported here on an elderly non-diabetes patient with renal insufficiency, who developed severe hyperglycemia after seven days of oral gatifloxacin administration. His advancing age and renal impairment were considered the significant contributing factors to this event. Without dose adjustment, 400 mg of gatifloxacin was prescribed and he developed severe hyperglycemia and acute renal failure 7 days after exposure.

Alterations in plasma glucose and insulin production have recently been documented with new generation fluoroquinolones, including gatifloxacin,

levofloxacin, and moxifloxacin<sup>(1-6)</sup>. The current package insert of gatifloxacin describes the possibility of both hypo- and hyperglycemic events<sup>(1)</sup>. The product information also cautions clinicians to monitor glucose levels when the drug is given to diabetic patients.

Gatifloxacin is the most likely possible cause of hyperglycemia in the presented patient. Normally hyperglycemic events usually develop 4–10 days after initial dosing. This is compatible with the presented case<sup>(7)</sup>. The patient's plasma glucose was normal before starting the medication and he developed severe hyperglycemia after 7 days of oral administration while his bronchitis improved. In addition, his hyperglycemia recovered after the authors stopped the medication.

Other possible contributing factors for this episode of severe hyperglycemia that should also be considered in the presented patient include undiagnosed diabetes, physical stress induced by infection, acute renal insufficiency on top of chronic renal failure, and drug-induced hyperglycemia. Physical stress is one of known precipitating factors of hyperglycemia. It is already known that release of glucagons and catecholamines during stress result in elevated plasma glucose levels<sup>(8,9)</sup>. Although the presented patient had been under significant physical stress from acute bronchitis on the day of admission, his random plasma glucose was still in the normal range (97 mg/dL). Furthermore, his bronchitis symptoms improved before hyperglycemia detected. Therefore, this stress-induced phenomenon does not seem to lead to the marked hyperglycemia.

The authors reviewed other potential drug-induced hyperglycemia in the presented patient. Two medications that can induce hyperglycemia were detected, carvedilol and hydrochlorothiazide. Their effects are through hypokalemia and a direct action on pancreatic beta-cell function can occasionally cause hyperglycemia in some patients<sup>(10,11)</sup>. However, the time course of their administration in the present case does not correlate with the onset of hyperglycemia. The presented patient had been taking these medications chronically prior to developing hyperglycemia, and his hyperglycemia improved after gatifloxacin withdrawal. Undiagnosed diabetes also requires consideration any time in a patient who develops this syndrome. In the presented case, even though he had normal fasting plasma glucose documented in his prior regular check up, his current HbA1c was 7.4%, which likely implies that the patient may have had some degree of impaired glucose tolerance over the previous 3 months or his recent high glucose levels may partly contribute to

this high level of HbA1c during the measurement. However, the plasma glucose was not elevated during this acute bronchitis attack at the time of admission. Therefore, the probable, previous abnormal glucose homeostasis in the presented case could not solely explain this significant hyperglycemia episode. Moreover, his euglycemia could be achieved easily without any medication. There have been independent case reports of hyperglycemia in patients taking gatifloxacin, with and without pre-existing diabetes mellitus. Initial reports focused on age as a contributing factor<sup>(12)</sup>. However, renal function that declines with age also appears to play an important role.

Old age and renal dysfunction were considered the significant contributing factors of abnormal glucose homeostasis in the presented case. Hyperglycemia and peripheral insulin resistance are common in acute renal failure. These findings are thought to be due to increases in the levels of glucagons, growth hormone, and catecholamines. Other contributing mechanisms include impairment in the degradation of glucagons and insulin as well as an increase in the secretion of inflammatory cytokines<sup>(9)</sup>. The presented patient had a further reduction in renal function, underlying chronic renal failure, when he presented. This was without an elevated glucose level. Acute renal insufficiency was detected later on, which was a result of volume depletion from severe hyperglycemia while being treated with gatifloxacin. Gatifloxacin is primarily eliminated through renal excretion of unchanged drug with no cytochrome P450-mediated metabolism<sup>(13)</sup>. In renal insufficiency, the drug clearance has been reported reduction up to 77%, whereas half-life of gatifloxacin in plasma may be extended to 40 hours in end-stage renal disease patient. It has also been found that systemic exposure was 4 times higher in patients with severe renal insufficiency. The literature suggests using a reduced dose for patients whose creatinine clearance falls below 40 mL/min and probably for patients aged more than 65 years. Reported patients had a mean age of 68.9 years with a mean creatinine clearance of 30.9 mL/min<sup>(12,14,15)</sup>. In addition to the risk factors of age and reduced creatinine clearance, the majority of patients had received an inappropriately high dose of gatifloxacin<sup>(12,14,15)</sup>. Therefore, it is suggested to adjust gatifloxacin dosing to 200 mg/d in patients with a creatinine clearance of <40 mL/min and serum glucose should be monitored<sup>(12)</sup>. Based on evidence from prior case reports and the drug's pharmacokinetic property, it is possible that the presented patient's declining renal function and receiving 400

mg/day orally without any adjustment for his renal function were associated with his drug reaction.

Gatifloxacin-induced changes in glucose homeostasis have been reported with increasing frequency since its release in 1999. Both hypo and hyperglycemia were documented. In 2002, 2 groups reported severe, symptomatic hypoglycemia related to gatifloxacin use in patients with type 2 diabetes mellitus who received oral hypoglycemic agents<sup>(6,16)</sup>. Additional reports of symptomatic hypoglycemia associated with gatifloxacin followed<sup>(5-7,17-23)</sup>, as well as reports of symptomatic severe hyperglycemia<sup>(7,12,14,15,24-26)</sup>. Studies have indicated that hypoglycemia probably occurs with a greater incidence than hyperglycemia. However, hyperglycemia should not be overlooked. Accumulating evidence suggests that gatifloxacin can cause hyperosmolar nonketotic hyperglycemia. Frothingham<sup>(7,27)</sup> presented a study on the issue of glucose homeostasis abnormalities (GHA). He used the US Freedom of Information Act to obtain all spontaneous adverse drug effect (ADE) reports filed with the US Food and Drug Administration (FDA) for the fluoroquinolones ciprofloxacin, gatifloxacin, levofloxacin, and moxifloxacin from November 1997 to September 2003. Five hundred and sixty-eight GHA reports were found, of which 25 indicated a fatality. They presented that gatifloxacin was associated with 80% of all quinolone GHA reports and 68% of them indicating a fatality. The incidence of GHA reports filed with the FDA demonstrated that gatifloxacin is the most common quinolone to be related to GHA (477 per 10 million scripts for gatifloxacin compared with 8 per 10 million scripts for the 3 other fluoroquinolones combined ( $p < 0.001$ )). They found that the majority of patients with fluoroquinolone-associated hypoglycemia were elderly diabetic patients receiving oral hypoglycemic agents, whereas the patients who developed fluoroquinolone-associated hyperglycemia were also elderly, but were usually not diabetics<sup>(7)</sup>. These published reports and other unpublished cases reported to regulatory agencies led to modifications of the product labeling<sup>(16)</sup>. In Japan, regulators required labeling to state that gatifloxacin is contraindicated in patients with diabetes mellitus<sup>(28)</sup>.

Until now, the exact mechanism of glucose homeostasis abnormalities (GHA) induced by gatifloxacin is still unknown, Saraya et al<sup>(29)</sup> demonstrated that gatifloxacin and tosufloxacin stimulated insulin secretion and inhibited potassium ATP channel currents in a dose-dependent manner, whereas levofloxacin had only a small effect. Further basic science studies are required to answer these questions.

## Conclusion

The authors reported here that the hyperglycemic adverse effect of oral gatifloxacin developed in a 73-year-old non-diabetic male patient. Although undiagnosed impaired glucose tolerance was not completely ruled out in the presented patient due to the evidence of a slightly increased HbA1c level during the admission, a subsequent follow-up showed that the fasting glucose levels were in the normal range. Renal insufficiency and advanced age are the important precipitating factors for this condition. The patient's renal insufficiency contributed to the hyperglycemia through the decreased clearance of gatifloxacin. Clinicians should become more aware of the glucose-altering effects of gatifloxacin, both hypo and hyperglycemia, as they have been reported in the literature. Dose adjustment should be routinely recommended for the patients who are elderly or have renal impairment.

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**ภาวะสูงอายุและไตเสื่อมเป็นปัจจัยให้เกิดภาวะน้ำตาลในเลือดสูงจากการใช้ยาแกติฟลอกซาซินในผู้ป่วยที่ไม่มีคามผิดปกติของระดับน้ำตาลมาก่อน**

**มูจรินทร์ โอวาทพารพร, วัลยา จงเจริญประเสริฐ**

รายงานการเกิดความผิดปกติของระดับน้ำตาลกลูโคสในผู้ป่วยที่ได้รับยาแกติฟลอกซาซินนี้พบมากขึ้นเรื่อย ๆ ต่อไปนี้เป็นรายงานผู้ป่วยชาย อายุ 73 ปี ไม่มีประวัติโรคเบาหวานมาก่อน มีโรคประจำตัวคือความดันโลหิตสูง โรคเนื้องอกของกระเพาะปัสสาวะชนิดพีไอโครโมไซโตมาซึ่งได้รับการรักษาโดยการผ่าตัดหายแล้ว โรคหัวใจโต และหัวใจล้มเหลวเรื้อรัง ไตเสื่อมโดยที่มีค่าครีเอตินินพื้นฐาน 1.7 มิลลิกรัม/เดซิลิตร และโรคเกาต์ ได้รับเข้ารักษาในโรงพยาบาลด้วยเรื่องหลอดลมอักเสบ ผู้ป่วยได้รับยาแกติฟลอกซาซินในขนาด 400 มิลลิกรัมต่อวัน โดยการรับประทานหลังจากได้รับยา 7 วันอาการหลอดลมอักเสบดีขึ้น แต่กลับพบว่าผู้ป่วย มีอาการปัสสาวะบ่อย หิวน้ำมากและอ่อนเพลีย ตรวจพบการทำงานของไตเลวลง โดยมีค่าครีเอตินินสูง 2.8 มิลลิกรัม / เดซิลิตร และระดับ น้ำตาลสูงถึง 903 มิลลิกรัม/เดซิลิตร ผู้ป่วยได้รับการรักษาโดยการหยุดยาปฏิชีวนะและได้รับการฉีดอินซูลินเข้า หลอดเลือด พบว่าระดับน้ำตาลผู้ป่วยลดลงมาสู่ปกติภายใน 8 ชั่วโมงโดยใช้อินซูลินขนาดต่ำ และติดตามระดับน้ำตาลก่อนอาหารพบว่ากลับมาเป็นปกติโดยไม่ต้องใช้ยาลดระดับน้ำตาลและอินซูลินอีกเลย ผลข้างเคียงที่เกิดขึ้นกับผู้ป่วยน่าจะเกิดจากการใช้ยาแกติฟลอกซาซิน โดยมีปัจจัยเกื้อหนุนคืออายุมากและการทำงานของไตที่ลดลง