Hypoglycemia and Levofoxacin: A Case Report

To the Editor—We report a case of an infrequent but potentially serious adverse effect of levofoxacin. The patient was an 86-year-old woman who lived in a nursing home. The patient has had hard-to-control type 2 diabetes mellitus for >40 years and has received treatment with 34 U of NPH insulin per day, occasionally supplemented with rapid insulin. The patient presented with renal insufficiency, with an estimated creatinine clearance value of 27.1 mL/min and chronic respiratory insufficiency, which required home oxygen administration. On 6 April 2007, the patient developed an episode of respiratory infection with fever, loose coughing, and worsening dyspnea, which made it necessary to increase the amount of oxygen that the patient received. She was treated with a regimen of levofoxacin (500 mg per 24 h). Three days after initiating treatment with levofoxacin, routine examinations revealed glycemic levels that were lower than those normally reported for the patient, who also experienced severe episodes of hypoglycemia (capillary glycemia, <70 mg/dL). After the fifth day, glycemic values remained low, even though the administration of insulin had been interrupted, with severe episodes of hypoglycemia. During the fifth day, 3 doses of glucagon (1 mg) were administered subcutaneously. On the 6th day, levofoxacin was discontinued. From this point on, the patient was not treated with insulin and continued to receive an intravenous perfusion of 10% glucose in saline solution and received 20 mL of 33% hypertonic glucose solution. From the 9th day onwards, glycemic values gradually returned to the normal range. Blood levels of levofoxacin 4 days after treatment discontinuation were 14 mg/dL (normal value, ≤5 mg/dL).

Several articles have associated the administration of fluoroquinolones with alterations in glucose metabolism. Gatifloxacin is the most commonly involved fluoroquinolone in hypoglycemic and hyperglycemic episodes [1–3]. A retrospective study reports a greater association of levofoxacin with episodes of hyperglycemia, compared with ceftriaxone [4]. The likelihood of developing hypoglycemia is significantly greater with gatifloxacin (OR, 4.3; 95% CI, 2.9–6.3) and levofoxacin (OR, 1.5; 95% CI, 1.2–2.0) than with macrolides [5].

A study that analyzed the levels of insulin in cultured hamster pancreatic islet cells exposed to gatifloxacin for a short period suggested that fluoroquinolones stimulate the release of insulin-blocking K\(^+\) ATP-dependent channels in the membrane of pancreatic cells, thereby triggering the onset of hypoglycemia. After long-term exposure to gatifloxacin, the pancreatic cell showed lower intracellular levels of insulin and subsequent interruption of insulin secretion. Because of this, episodes of hyperglycemia were more common in the long term [6]. Ishiwata et al. [7] studied the effect of levofoxacin on glycemia in rats, finding that levofoxacin caused hypoglycemia or hyperglycemia, depending on the dose of the drug administered.

Gatifloxacin is mainly eliminated through the kidneys, and it appears that diminished clearance of gatifloxacin is the main predictor of glycemic alterations [6]. Our patient experienced renal insufficiency, with an estimated creatinine clearance of 27.1 mL/min. Even though the majority of cases of hypoglycemia due to levofoxacin use have been reported in patients taking oral antidiabetic agents, specifically sulphonylureas [4, 8, 9], there have also been cases in patients who receive insulin or in diabetic patients who are solely undergoing dietary treatment [5]. To the best of our knowledge, this is the first published case of hypoglycemia caused by levofoxacin in a diabetic patient treated exclusively with insulin.

Acknowledgments

Levofoxacin and Hypoglycemia

To the Editor—Levofoxacin has been previously reported to cause hypoglycemia in 4 patients [1–4]. In 2 of these instances, delays in recognizing the etiology of the hypoglycemia led to unfortunate consequences [1, 3]. An elderly surgical patient in our care recently died of recurrent hypoglycemia induced by levofoxacin. This prompted us to undertake a questionnaire survey of clinicians in our hospital, which is a university-affiliated teaching hospital. We queried them on the frequency of prescriptions for levofoxacin and gatifloxacin, the indications for their use, whether they were aware of its hypoglycemic adverse effects, and whether they could recall any unexplained hypoglycemic events in patients receiving levofoxacin or gatifloxacin in the previous 6 months.

Nineteen completed questionnaires were obtained from 138 clinicians. Most (37 of 97) were received from clinicians in internal medicine and its allied specialties. Others were from specialists in surgery (26), gynecology (13), critical care (9), orthopedics (8), and otorhinolaryngology (4). More than 58% of respondents prescribed levofoxacin at least once in the preceding month, and 19% were considered heavy prescribers (>3 prescriptions/week). Gatifloxacin had been prescribed by 72% of respondents in the previous month, and 14% were considered heavy prescribers. The most common reason for prescribing levofoxacin and gatifloxacin was lower respiratory infection (42%) and urinary tract infection (30%), respectively. Seventy-nine respondents (42%) and urinary tract infection (30%) were considered heavy prescribers of levofoxacin (all of whom were from internal medicine and allied specialties) were unaware that it could cause hypoglycemia. More strikingly, 17 (94.4%) of the 18 heavy prescribers of levofoxacin (all of whom were from internal medicine and allied specialties) were unaware that it could cause hypoglycemia. There was a better awareness about the potential adverse effect of hypoglycemia for levofoxacin among surgical colleagues because of the recent death of a surgical patient caused by levofoxacin-induced hypoglycemia. With regard to gatifloxacin, the 14 heavy prescribers were distributed across all departments, and 8 (57.1%) of the 14 were aware of the possibility of hypoglycemia. Six respondents (6.2%) could recall unexplained hypoglycemia in patients receiving levofoxacin, and 14 (14.4%) of 97 could recall hypoglycemic episodes in patients receiving gatifloxacin in the preceding 6 months.

This survey reveals that both levofoxacin and gatifloxacin are commonly prescribed antibiotics in our hospital. Despite their frequent use, awareness about the potential hypoglycemic effect is poor. On the basis of physician recall of unexplained hypoglycemia over the previous 6 months, it appears that hypoglycemia due to levofoxacin use is much more common than is reported in literature. There is better documentation of the dysglycemic adverse effects of gatifloxacin, and thus, better awareness. Improved awareness about hypoglycemia associated with levofoxacin use is essential to prevent further unfortunate consequences.

Acknowledgments

Potential conflicts of interest. N.S. and J.J.J.: no conflicts.

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Risk of Early Virological Failure of Once-Daily Tenofovir-Emtricitabine plus Twice-Daily Nevirapine in Antiretroviral Therapy–Naïve HIV-Infected Patients

To the Editor—The combination of tenofovir, emtricitabine, and nevirapine is recommended as first-line treatment for...