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A Rare but Serious Side Effect of Levofloxacin

Hypoglycemia in a geriatric patient

Drugs should always be considered in the differential diagnosis of hypoglycemia. Fluoroquinolones have rarely been associated with hypoglycemia (1,2). Levofloxacin, which belongs to the fluoroquinolone group of antibiotics, has previously been reported to cause hypoglycemia in only one patient who was also receiving oral antidiabetic drugs (2). Herein, we describe an elderly patient with hypoglycemia associated with levofloxacin therapy who did use oral antidiabetic drugs or insulin.

A 64-year-old female with type 2 diabetes treated only by diet was interned for urinary infection and pneumonia. She had no history of malabsorption or oral intolerance. The patient's weight was 84 kg, and she was 157 cm tall (corresponding to a BMI of 34.1 kg/m²). Her current medications included coraspin, omeprazole, and atorvastatin. Cefuroxime 3 × 750 mg/day i.v. was started. During cefuroxime therapy, her blood glucose levels were within normal limits with diet. C-reactive protein level was not decreased. On the 3rd day of treatment, cefuroxime was replaced with levofloxacin (500 mg/day) because of unresponsiveness. During treatment with levofloxacin, the symptoms of diseases diminished significantly, but the patient complained of generalized weakness. On the 2nd day of levofloxacin therapy, the patient became lethargic and disoriented. Blood pressure was 126/72 mmHg, heart rate was 82 bpm and regular, and body temperature was normal. Meningeal irritation signs were absent, and pupils were intermediate, symmetric, and reactive. Optic fundi were normal, and no focal neurologic deficit was de-

tected. Other physical findings were unremarkable. Her blood glucose level was measured as 32 mg/dl. The simultaneous blood insulin level was 6.7 IU (normal range 5–25 IU). Other routine hematological and biochemical blood tests were within normal range. Electrocardiography was also normal. A 30% dextrose infusion was started, and the patient thereafter became fully conscious without any neurologic deficit. Although she did not take any insulin during dextrose infusion, her consequent blood glucose levels were measured as 54 and 62 mg/dl in the 1st and following the 4th h. On the 3rd day of levofloxacin treatment, another hypoglycemic episode was observed. During treatment with levofloxacin, she did not change her usual daily diet regimen. Levofloxacin was stopped, and we continued treatment with piperacillin tazobactam. No further episodes of hypoglycemia were observed during follow-up period.

The symptomatic hypoglycemia in our patient developed 1 day after initiating treatment with levofloxacin. Since no other apparent cause for hypoglycemia was found, levofloxacin was the most likely etiology of this dangerous and potentially fatal glucose abnormality. Levofloxacin is an increasingly popular broad-spectrum antibiotic. In general, it has an excellent safety profile and is considered safe in patients with penicillin or cephalosporin allergy (3). Published reports about adverse effects of fluoroquinolones are available for ciprofloxacin, gatifloxacin, clinafloxacin, and only one case of levofloxacin (2,4,5).

The previously published reports about fluoroquinolone-associated hypoglycemia consisted of elderly patients with a history of type 2 diabetes, renal dysfunction, and receiving oral sulfonylureas (2,4). Our patient also had only diabetes. Consistent with most published case reports, the hypoglycemia in our patient was documented within 24 h of levofloxacin administration, and intravenous dextrose was required for correction of hypoglycemia. Other factors such as poor oral intake or renal dysfunction that could have contributed to the profound and prolonged hypoglycemia were not present in our patient. The mechanisms by which fluoroquinolones cause hypoglycemia are not fully understood. In one study, increased rat pancreatic islet cell insulin release was claimed to be the mechanism. This process was inhibited by drugs that antagonized adenosine triphosphate-sensitive K⁺ channels, sug-

gesting that this channel is involved (6). Use of the Naranjo ADR Probability Scale (7) indicated a probable relationship between the adverse effect of hypoglycemia and levofloxacin therapy in this patient.

This case showed that even one dose of levofloxacin might be associated with significant and even fatal complications in geriatric patients without any previous renal dysfunction or impaired oral intake. To our knowledge, this is the first case of hypoglycemia related to levofloxacin in an elderly diabetic patient not using any oral antidiabetic drugs or insulin. The purpose of this letter is to caution physicians dealing with geriatric patients against the inappropriate use of fluoroquinolones in these patients, especially in those with diabetes, since they may have a greater tendency to hypoglycemia. It might be important to monitor blood glucose levels early in the course of therapy.

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Cigarette Smoking Affects Urinary Liver-Type Fatty Acid-Binding Protein Concentration in Patients With Early Diabetic Nephropathy

Cigarette smoking causes a decrease in the glomerular filtration rate in diabetic patients with normal renal function, independent of confounding factors including severe proteinuria (1). It increases the risk of microalbuminuria and accelerates the progression from microalbuminuria to overt proteinuria as well as the progression of renal failure in patients with type 2 diabetes (2). It is widely accepted that the rate of functional decline correlates with the degree of renal tubulointerstitial fibrosis. Previous studies have shown that renal function in patients with type 2 diabetes correlates better with tubular changes than with glomerular pathology (3). Further studies on tubulointerstitial injury in patients with diabetic nephropathy may provide additional insight into the pathogenesis of diabetic nephropathy and lead to the identification of therapeutic targets. Liver-type fatty acid-binding protein (L-FABP) is expressed in the proximal tubules, where it plays a key role in fatty acid metabolism. We and other investigators reported that urinary L-FABP may be a useful clinical marker for type 2 diabetic nephropathy (4–6). However, little is known about the effect of cigarette smoking on the urinary L-FABP level.

Fifty type 2 diabetic patients with microalbuminuria (28 men and 22 women, mean age 50.0 years), including 30 smokers (18 men and 12 women) and 20 nonsmokers (10 men and 10 women), were enrolled in the present study. No patient had a serum creatinine (Cr) level >1.2 mg/dl. Urinary L-FABP levels were measured by an enzyme-linked immunoassay kit as described previously (4–6). The urinary

L-FABP level was significantly higher in smokers ($20.5 \pm 10.5 \mu\text{g/g Cr}$) than in nonsmokers ($10.5 \pm 5.5 \mu\text{g/g Cr}$) ($P < 0.05$). The smokers were divided into two groups: those who stopped smoking ($n = 10$, group A) and those who continued smoking ($n = 20$, group B). The angiotensin receptor blocker, ACE inhibitor, statin, antidiabetic drugs, and antiplatelet drugs used in the two groups were similar. After 24 months, the urinary L-FABP level in group A decreased significantly from 21.5 ± 10.0 to $13.5 \pm 8.0 \mu\text{g/g Cr}$ ($P < 0.05$); however, that in group B increased significantly from 20.0 ± 11.0 to $27.5 \pm 15.5 \mu\text{g/g Cr}$ ($P < 0.05$). These data suggest that cigarette smoking may be associated with tubulointerstitial injury in patients with early diabetic nephropathy.

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The Prevalence and Management of Diabetes in Rural India

Very high levels of diabetes have been reported in urban areas of India (1), but few data are available for rural regions where >70% of the population lives. Data from a new large-scale survey done in 2005 suggest rural India may soon experience the same epidemic of diabetes. A total of 4,535 individuals aged ≥ 30 years (response rate 81%, mean age 46.8 years) were sampled at random age and sex strata from 20 villages representative of Godavari, a developing rural area of Andhra Pradesh. Data were collected using a structured questionnaire and a brief physical examination with fasting finger-prick blood glucose measured in all participants using B-Braun USV meters (Melsungen, Germany). Fasting venous samples were also done in a random subsample of 1,070 individuals. Estimates of diabetes prevalence for the 20 villages were calculated by applying sampling weights derived from a census done in 2004 with diabetes defined by disease history and/or fasting glucose of 7.0 mmol or over.

On the basis of the finger-prick measurements, the prevalence of diabetes was 13.2% (95% CI 12.1–14.3), of which 6.4% (5.6–7.2) were known and 6.8% (5.9–7.6) were previously undiagnosed. A further 15.5% (14.2–16.8) had impaired fasting glucose (Table 1). Overall estimated mean fasting glucose levels from USV meters was 5.8 mmol/l (5.7–5.9). In the subsample, venous blood measurements gave a lower estimated mean glucose of 5.6 mmol/l (5.4–5.7). The systematically lower levels for the venous samples likely reflect the delay in assay, consequent upon transport of the samples to the local laboratory, and the higher finger-prick estimates are probably a more accurate reflection of the true prevalence of diabetes in this community.

Of those with known diabetes, 67% (61–73) were taking oral hypoglycemic therapy, 3% (1–5) were using insulin, and 46% (40–53) were taking blood pressure-lowering agents. These relatively high levels of treatment suggest that even in fairly poor rural settings, proven preventive therapies are accessible to many and that strategies to improve detection