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Fluoroquinolone-associated dysglycemia: A case of levofloxacin-induced hypoglycemia in renal insufficiency

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Abstract
Levofloxacin is a widely prescribed third-generation fluoroquinolone antibiotic effective against respiratory and urinary tract infections. Though generally safe, it has been rarely associated with life-threatening adverse effects such as severe hypoglycemia. We report the case of a 69-year-old retired school teacher with chronic kidney disease and hypertension who developed prolonged, refractory hypoglycemia after initiation of levofloxacin for an acute exacerbation of chronic bronchitis. Despite supportive care including intravenous dextrose and glucagon, hypoglycemia persisted until the antibiotic was discontinued, resulting in full recovery. This case underlines the importance of heightened clinical suspicion for rare but serious metabolic complications of levofloxacin, especially in vulnerable populations with renal impairment.

Keywords: Levofloxacin, fluoroquinolones, hypoglycemia, adverse drug reaction, chronic kidney disease, pharmacovigilance

Introduction

Levofloxacin, the L-isomer of ofloxacin, is a third-generation fluoroquinolone antibiotic with a broad spectrum of activity against Gram-positive, Gram-negative, and atypical pathogens [1]. Its excellent bioavailability and favorable pharmacokinetic profile have made it a cornerstone in the treatment of community-acquired pneumonia, acute bacterial sinusitis, urinary tract infections, and acute exacerbations of chronic bronchitis [2]. While generally considered to have a favorable safety profile, the widespread use of fluoroquinolones has led to an increasing recognition of their potential to cause rare but severe adverse drug reactions (ADRs), including tendinopathy, aortic dissection, and central nervous system disturbances [3].

Among the most critical metabolic ADRs are disturbances in glucose homeostasis, manifesting as either hyperglycemia or, more alarmingly, severe hypoglycemia [4]. This phenomenon, known as dysglycemia, is a class effect of fluoroquinolones, though the incidence and severity vary between agents [5]. Gatifloxacin, for instance, was associated with such a high rate of severe dysglycemia that its use has been severely restricted in many countries [6]. Although less common with levofloxacin, cases of profound and life-threatening hypoglycemia have been documented, particularly in patients with predisposing risk factors [7]. The primary risk factors include advanced age, diabetes mellitus (especially when treated with insulin or sulfonylureas), and, most notably, renal impairment, which can lead to drug accumulation [8].

We present the case of a non-diabetic elderly male with stage 3 chronic kidney disease (CKD) who developed severe, refractory, and prolonged hypoglycemia following the initiation of high-dose oral levofloxacin. This report aims to highlight the critical link between levofloxacin, renal function, and severe hypoglycemia, review the underlying pathophysiology, and underscore the importance of pharmacovigilance and appropriate dose adjustment in vulnerable patient populations.

Case Presentation

A 69-year-old retired male school teacher presented to the emergency department with sudden-onset confusion, diaphoresis, and tremors, first observed by his wife. His medical history was significant for stage 3 chronic kidney disease (baseline estimated Glomerular Filtration Rate [eGFR] of 38 mL/min/1.73m²), hypertension managed with amlodipine, and a healed peptic ulcer for which he took pantoprazole. He had no personal or family history of diabetes mellitus, prior hypoglycemic episodes, or pre-existing cognitive deficits.

Four days prior to this presentation, he had been discharged from another hospital after being treated for an acute exacerbation of chronic bronchitis. His discharge medications included a new prescription for oral levofloxacin at a dose of 750 mg once daily, in addition to his regular medications.

Upon arrival at our facility, his vital signs were stable: blood pressure was 146/82 mmHg, heart rate was 68 beats per minute, respiratory rate was 17 breaths per minute, and his oxygen saturation was 97% on ambient air. His temperature was 36.8 °C. A neurological examination revealed mild confusion and disorientation to time and place, but no focal neurological deficits were identified. A point-of-care capillary blood glucose measurement was critically low at 38 mg/dL (2.1 mmol/L).

The patient was immediately administered an intravenous bolus of 40 mL of 50% dextrose, which led to a transient improvement in his mental status. However, a repeat blood glucose measurement 30 minutes later showed recurrent hypoglycemia at 55 mg/dL (3.1 mmol/L). Admission laboratory results were as follows: serum creatinine 1.5 mg/dL (consistent with his CKD baseline), blood urea nitrogen 45 mg/dL, sodium 139 mEq/L, potassium 3.3 mEq/L, and albumin 3.2 g/dL. Liver function tests and a random cortisol level were within normal limits. A critical blood sample drawn during a hypoglycemic episode revealed an inappropriately elevated serum insulin level of 16 µIU/mL (normal <3 µIU/mL during hypoglycemia) and a corresponding C-peptide level of 3.8 ng/mL (normal 1.1-4.4 ng/mL), confirming endogenous hyperinsulinism. A urine toxicology screen was negative for sulfonylureas and meglitinides.

His management was challenging. Over the first 24 hours, he required multiple boluses of 50% dextrose (totaling 75 g), two separate 1 mg intramuscular injections of glucagon, and a continuous intravenous infusion of 10% dextrose at 50 mL/hour. Despite these aggressive measures, his blood glucose remained labile, fluctuating between 42 mg/dL and 82 mg/dL, with recurrent symptomatic episodes requiring intervention.

A thorough review of his medications identified levofloxacin as the most likely offending agent, given the clear temporal association between its initiation and the onset of symptoms. The drug was immediately discontinued, and he was started on an alternative antibiotic regimen guided by sputum culture sensitivities. Within 48 hours of levofloxacin cessation, his hypoglycemic episodes resolved completely. His blood glucose levels stabilized in the range of 96-108 mg/dL without the need for supplemental dextrose. The patient's cognitive function returned to his baseline, and he was discharged home after a four-day hospital stay. At a two-week follow-up appointment, he remained neurologically intact and normoglycemic.

Discussion

This case illustrates a severe, life-threatening adverse drug reaction to levofloxacin in a patient with multiple, well-established risk factors. The temporal relationship between the drug's administration and the onset of refractory hypoglycemia, coupled with the rapid resolution of symptoms upon its discontinuation, strongly supports a causal link. The Naranjo adverse drug reaction probability scale yields a score of 7, indicating a "probable" adverse reaction [9]. The patient's presentation with endogenous hyperinsulinism (elevated insulin and C-peptide levels during hypoglycemia) is consistent with the known mechanism of fluoroquinolone-induced hypoglycemia.

Pathophysiology of Fluoroquinolone-Induced Hypoglycemia

The primary mechanism by which fluoroquinolones, including levofloxacin, induce hypoglycemia involves their interaction with pancreatic β-cells [10]. These drugs are known to block ATP-sensitive potassium (K-ATP) channels in the β-cell membrane [11]. The K-ATP channel plays a crucial role in glucose-stimulated insulin secretion.5 In a resting state, these channels are open, allowing potassium efflux and maintaining a hyperpolarized membrane potential, which prevents insulin release [12]. When fluoroquinolones bind to and block these channels, potassium efflux is inhibited. This leads to membrane depolarization, which in turn opens voltage-gated calcium channels [13]. The subsequent influx of calcium ions into the cell triggers the exocytosis of insulin-containing granules, resulting in a state of unregulated insulin secretion and subsequent hypoglycemia [14]. This mechanism is notably similar to that of sulfonylurea drugs, which are widely used to treat type 2 diabetes by targeting the sulfonylurea receptor 1 (SUR1) subunit of the K-ATP channel [15]. This explains the clinical picture of hyperinsulinemic hypoglycemia observed in our patient and others reported in the literature.

The Critical Role of Risk Factors

While levofloxacin-induced hypoglycemia is rare, its occurrence is not random. The risk is significantly amplified in patients with specific vulnerabilities, several of which were present in our patient.

1. **Chronic Kidney Disease (CKD):** This is arguably the most significant risk factor. Levofloxacin is primarily eliminated via the kidneys, with approximately 87% of the dose excreted unchanged in the urine [16]. In patients with impaired renal function, the drug's half-life is prolonged, leading to its accumulation and higher-than-intended plasma concentrations [17]. This supratherapeutic exposure dramatically increases the risk of concentration-dependent adverse effects, including its effect on pancreatic K-ATP channels. The prescribing information for levofloxacin explicitly recommends dose reduction for patients with a creatinine clearance below 50 mL/min [1]. Our patient, with an eGFR of 38 mL/min/1.73m², was prescribed a standard high dose of 750 mg daily, which was inappropriate for his level of renal function and likely the primary driver of this severe ADR. A dose of 750

mg every 48 hours would have been more appropriate [18]. This highlights a critical gap in medication reconciliation and dose adjustment.

2. **Advanced Age:** Elderly patients are inherently more susceptible to ADRs due to a combination of factors. These include age-related decline in renal function (even with normal serum creatinine), altered pharmacodynamics, polypharmacy leading to potential drug-drug interactions, and diminished physiological reserves to counteract metabolic insults like hypoglycemia [19, 20]. The neuroglycopenic symptoms (confusion, tremors) can also be mistaken for other geriatric syndromes, such as delirium or stroke, potentially delaying diagnosis.
3. **High Dose of Levofloxacin:** The patient was prescribed 750 mg daily, a dose typically reserved for severe infections like hospital-acquired pneumonia. Higher doses of fluoroquinolones have been associated with a greater risk of dysglycemia compared to lower doses [21]. The combination of a high dose with pre-existing renal insufficiency created a "perfect storm" for drug accumulation and toxicity.

Literature Review and Comparison with Other Fluoroquinolones

The association between fluoroquinolones and dysglycemia has been recognized for over two decades. Gatifloxacin was most strongly implicated, with numerous reports leading to a "black box" warning from the FDA and its eventual withdrawal from the market in the United States [22]. Studies have shown that the propensity to cause dysglycemia varies among different fluoroquinolones, likely due to differences in their chemical structure and affinity for the K-ATP channel [23]. Moxifloxacin and levofloxacin are considered to have an intermediate risk, while ciprofloxacin appears to have the lowest risk of causing hypoglycemia [5, 24].

A large population-based study found that levofloxacin use was associated with a significantly increased risk of emergency room visits or hospitalization for hypoglycemia, particularly in patients also taking antidiabetic drugs [25]. However, as our case demonstrates, this severe ADR can also occur in non-diabetic individuals, a scenario that is less common but arguably more dangerous, as there is a lower index of suspicion for hypoglycemia. Several other case reports have documented levofloxacin-induced hypoglycemia in non-diabetic patients with renal failure, further corroborating our findings [26, 27]. The refractory nature of the hypoglycemia in our patient, requiring continuous dextrose infusion and glucagon, is also a recurrent theme in published cases, underscoring the severity of the insulin over-secretion driven by the accumulated drug [28].

Clinical and Prescribing Implications

This case provides several crucial learning points for clinicians. First, it emphasizes the absolute necessity of medication dose adjustment based on renal function. Before prescribing drugs that are renally cleared, especially those with a narrow therapeutic index or potential for severe ADRs, clinicians must calculate the patient's estimated GFR and consult prescribing guidelines [29]. Automatic stop-alerts and pharmacist-led medication reviews within electronic health records could serve as important safety nets to prevent such prescribing errors.

Second, a high index of suspicion for drug-induced hypoglycemia must be maintained when a patient on levofloxacin, particularly an elderly individual with CKD, presents with altered mental status, diaphoresis, or other neurological symptoms. These symptoms should prompt an immediate point-of-care glucose test.

Third, when managing such cases, clinicians should be prepared for prolonged and refractory hypoglycemia. The half-life of levofloxacin is approximately 6-8 hours in healthy individuals but can be extended to over 40 hours in patients with severe renal impairment [17]. Therefore, the hypoglycemic effects may persist for several days after the drug is discontinued, requiring sustained glucose monitoring and supportive care.

Finally, this case reinforces the importance of pharmacovigilance and reporting ADRs. Documenting and publishing such cases contributes to a better understanding of the real-world safety profile of medications and helps inform clinical practice and regulatory guidelines [30].

Conclusion

Levofloxacin is a potent and valuable antibiotic, but its use is not without risk. This case report details a severe and life-threatening episode of refractory hyperinsulinemic hypoglycemia in a non-diabetic elderly patient with chronic kidney disease, precipitated by an inappropriately high dose of levofloxacin. The pathophysiology is directly related to the drug's blockade of pancreatic K-ATP channels, an effect greatly potentiated by drug accumulation due to impaired renal clearance.

This case serves as a powerful reminder of fundamental prescribing principles: always consider the patient's renal function, adjust medication doses accordingly, and maintain a high level of vigilance for potential adverse drug reactions, especially in vulnerable populations. The presentation of new neurological symptoms in an elderly patient on levofloxacin should immediately raise suspicion for hypoglycemia. Early recognition of this adverse effect and prompt discontinuation of the offending agent are the most critical steps in management and are essential for preventing severe morbidity and mortality. Ultimately, a cautious and individualized approach to prescribing fluoroquinolones is paramount to maximizing their therapeutic benefit while minimizing the risk of rare but devastating harm.

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Authors' Contributions

Both authors have contributed equally to data collection, interpretation, and manuscript preparation

Conflict of Interest

The authors declare no conflict of interest.

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