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Case Report

Pharmacology Section

# Levofloxacin-induced Fatal Hypoglycaemia in a Non-diabetic Patient: A Case Report

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## ABSTRACT

Levofloxacin, a broad-spectrum, third-generation fluoroquinolone antibiotic, is rarely reported to cause life-threatening adverse effects, such as severe hypoglycaemia resulting in a coma. This case concerns hypoglycaemia in an elderly, non-diabetic patient induced by levofloxacin. A 61-year-old male patient was admitted with severe hypoglycaemia. Past medical history revealed treatment with levofloxacin for pneumonia. During the hospital stay, the patient was treated with multiple doses of 25 g dextrose 50% (D50), 2 doses of 1 mg glucagon, and a continuous infusion of dextrose 10% (D10). The patient was discharged on the sixth day of admission in a stable condition with no clinical symptoms. Clinicians must be aware of this lesser-known adverse effect to ensure quick recognition and treatment with the proper adjuncts.

**Keywords:** Diabetes, Fluoroquinolones, Hypoglycaemia, Levofloxacin

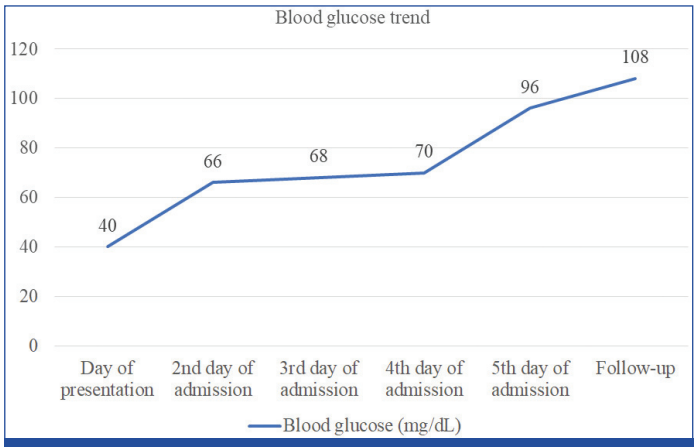
## CASE REPORT

A 61-year-old male patient with a medical history of chronic kidney disease and hypertension presented to the outpatient department of the hospital with symptoms of headache, dizziness, sweating, anxiety, and confusion over the past two days. On general examination, the patient was mildly stuporous. His blood pressure was 152/94 mmHg, pulse rate 72 beats/minute, respiratory rate 14/minute, and body temperature 97.6 F. Elementary and cardiorespiratory system examinations did not reveal any abnormalities. However, his blood glucose level was 40 mg/dL, indicating hypoglycaemia. The patient was treated with 25 gm of intravenous dextrose 50% (D50), which improved his mental status, but his blood glucose level remained low at 62 mg/dL. Consequently, he was admitted to the hospital.

The patient had a history of chronic kidney disease but no significant family history. Two weeks prior, he had been admitted to another hospital with symptoms of worsening dyspnea, cough, fever, and fatigue. At that time, he was diagnosed with pneumonia and acute renal failure, with a serum creatinine level of 3.96 mg/dL. He received treatment with corticosteroids (prednisone 40 mg twice daily), diuretics (furosemide 40 mg intravenous), and levofloxacin 500 mg once daily for seven days. Upon discharge, he was prescribed oral levofloxacin 500 mg once daily, while all other medications were discontinued. The patient had been taking levofloxacin regularly for the past five days before presenting to the hospital. He also had a regular intake of losartan 50 mg daily and spironolactone 25 mg daily for hypertension.

Initial laboratory tests revealed hypokalemia (serum potassium level of 2.7 mEq/L), hyponatremia (serum sodium level of 138 mEq/L), hypoalbuminemia (albumin level of 2.2 g/dL), and hypoglycaemia (blood glucose level of 66 mg/dL).

Levofloxacin was discontinued, and the patient received two doses of 1 mg glucagon, four boluses of dextrose 50%, and a continuous infusion of dextrose 10% (D10) over the next two days due to persistent hypoglycaemia. On the fourth day, the patient continued to receive the D10 infusion. After four days, his blood glucose levels returned to baseline (96 mg/dL on the fifth day) [Table/Fig-1]. He was ultimately discharged on the sixth day in stable condition with no clinical symptoms and was instructed to return for a follow-up after one week. During the follow-up, the patient remained stable, with no active clinical symptoms, and his blood glucose levels were within normal limits (108 mg/dL). This suggests that the most likely diagnosis was levofloxacin-induced hypoglycaemia.




**[Table/Fig-1]:** Blood glucose trend of the patient with hypoglycaemia.

## DISCUSSION

Levofloxacin is a broad-spectrum, third-generation fluoroquinolone antibiotic used to treat various bacterial infections [1,2]. Fluoroquinolones, known for their high oral bioavailability and excellent tissue penetration, are a widely prescribed as broad-spectrum antibiotics [3]. They are generally considered safe with few adverse effects. While levofloxacin is usually well-tolerated, it can rarely cause life-threatening adverse effects, including severe hypoglycaemia leading to coma [4,5]. Levofloxacin-induced hypoglycaemia is a rare reported side effect, and its exact mechanism is unknown but is believed to involve the blockage of adenosine 5'-triphosphate-sensitive potassium channels in pancreatic beta-cell membranes [6]. Currently, there are no specific treatment options available for this adverse effect. This case report describes a rare occurrence of life-threatening and refractory hypoglycaemia induced by levofloxacin in an elderly non-diabetic patient.

In the differential diagnosis of hypoglycaemia, drug-induced causes should always be considered. Fluoroquinolone-induced hypoglycaemia is a rare but known fatal adverse effect, and levofloxacin has been reported as the cause of hypoglycaemia in several published case reports [7-10]. In some cases, delays in identifying the cause of hypoglycaemia have led to unfavourable

outcomes. This case report contributes to the emerging data documenting levofloxacin as a cause of hypoglycaemia.

When being treated with levofloxacin, certain risk factors may predispose a patient to develop hypoglycaemia, such as concurrent use of insulin or sulfonylureas, advanced age, and renal insufficiency [11,12]. The patient in this case had no diabetes, was not taking insulin or any other oral hypoglycaemic medications, but did have chronic kidney disease. Several articles have linked fluoroquinolone administration, particularly gatifloxacin, to alterations in glucose metabolism [13]. Unlike other quinolones, there are no randomised controlled trials evaluating the incidence of levofloxacin-induced hypoglycaemia. However, a retrospective comparative study by Mohr et al., found a higher probability of hypoglycaemia with levofloxacin (OR, 1.5; 95% CI, 1.2-2.0) and gatifloxacin (OR, 4.3; 95% CI, 2.9-6.3) compared to macrolides [14].

The mechanism behind fluoroquinolone-induced hypoglycaemia has not yet been fully elucidated. However, studies using animal models have provided some evidence of the pharmacodynamic pathways that are believed to regulate insulin secretion [3]. These studies offer potential explanations for this clinical condition in addition to the known pharmacokinetic profile of levofloxacin.

Pancreatic β-cells' adenosine triphosphate-sensitive potassium channels (KATP) play a crucial role in detecting blood glucose levels and causing insulin release to maintain euglycaemia [15,16]. According to in-vitro studies, fluoroquinolones block these ATP-sensitive potassium channels, causing membrane depolarisation, which leads to calcium influx through voltage-gated calcium channels and boosts insulin secretion [17,18]. This effect has been demonstrated in a mouse model [19]. When sulfonylureas bind to their receptors (sulfonylurea receptor 1 subunit) located on these KATP channels, similar molecular events occur. As a result, the same downstream signaling is triggered, and calcium signaling causes the exocytosis of insulin secretory granules [20]. At a cellular level, the KATP channels of the pancreatic β-cell consist of a total of eight subunits (four SUR1 and four Kir6.2) [21]. In their study, Saraya A et al., found that gatifloxacin, levofloxacin, and temafloxacin specifically inhibit the Kir6.2 subunits of these channels in the pancreatic β-cells [18]. Gatifloxacin and temafloxacin have higher inhibitory potential on the Kir6.2 subunit compared to levofloxacin [22]. This explains why most cases of fluoroquinolone-induced hypoglycaemia have been reported with gatifloxacin rather than levofloxacin [12,14]. Further studies are needed to understand any potential unidentified biochemical trigger variables, as the risks of hypoglycaemia vary with different fluoroquinolones reported in the literature [23].

Under normal circumstances, the body's physiological mechanisms can compensate for a reduction in blood glucose levels. Generally, a decrease in blood glucose levels causes the pancreas to reduce insulin secretion and increase glycogenolysis in the liver. However, malnourished patients, such as elderly individuals, may not have sufficient glycogen reserves to mobilise in response to fluoroquinolone-induced hypoglycaemia [24]. In addition, the inability to compensate adequately and declining renal function in elderly people may result in decreased drug clearance. This explains why hypoglycaemia caused by fluoroquinolones is more frequently reported in the elderly.

Although levofloxacin was appropriately dosed for pneumonia in the patient, they did have risk factors (elderly with acute renal failure). This could have led to the accumulation of levofloxacin due to reduced renal clearance and a more prominent dose-dependent pharmacodynamic effect.

In this patient, hypoglycaemia was documented within 72 hours of levofloxacin administration, whereas most published case reports of levofloxacin-induced hypoglycaemia report a duration of 24-48 hours [25]. In the current case, the administration of levofloxacin coincided with the episode of fatal hypoglycaemia (refractory hypoglycaemia with neurological manifestations), and the condition resolved after discontinuing levofloxacin and administering dextrose and glucagon.

Concurrent drugs should also be evaluated for their potential to cause a hypoglycaemic episodes. The patient was already taking losartan and spironolactone due to comorbidities. However, these drugs have not been documented to cause hypoglycaemia when given separately or as a potential drug-drug interaction.

There are no specific treatments to reverse hypoglycaemia induced by fluoroquinolones [3]. Supportive care treatments, such as administering dextrose and glucagon, are the mainstay of treatment. However, the temporary elevation of serum glucose from these treatments is offset by rebound hypoglycaemia, which can occur in patients taking drugs like sulfonylureas that affect pancreatic β-cell KATP channels [26]. Rebound hypoglycaemia particularly occurs in patients with intact pancreatic function due to the additional glucose stimulating further insulin release [27,28]. This phenomenon of rebound hypoglycaemia may also occur with fluoroquinolones, given the similarity of their biological mechanisms to sulfonylureas. Some previously reported cases of fluoroquinolone-induced hypoglycaemia have been successfully treated with octreotide [3,29]. Octreotide is a potent synthetic analog of somatostatin, an inhibitory peptide hormone [27]. When octreotide binds to G-protein somatostatin-2 receptors on β cells of the pancreas, it keeps voltage-gated calcium channels closed, inhibiting calcium influx into the cell and preventing insulin release. This mechanism operates downstream of the KATP channel, blocking the cascade of molecular signaling induced by sulfonylureas and fluoroquinolones [26].

In a questionnaire survey conducted by Singh N and Jacob JJ to evaluate clinicians' awareness of the hypoglycaemic adverse effects of levofloxacin and gatifloxacin, it was found that nearly 80.4% of the participants were unaware that levofloxacin could cause hypoglycaemia [13]. This indicates that despite being a frequently used antibiotic, clinicians have poor awareness of the potential hypoglycaemic effect of levofloxacin. It is crucial to raise awareness about hypoglycaemia induced by levofloxacin to prevent unfortunate consequences. Clinicians should be aware of the risk factors for this adverse effect, as hypoglycaemia has the potential to cause significant morbidity and mortality. They should also increase monitoring or consider alternative treatments [30].

A re-challenge study with levofloxacin was not performed in our patient. The World Health Organisation-Uppsala Monitoring Centre (WHO-UMC) scale was used to assess the causality of this suspected Adverse Drug Reaction (ADR) [31]. According to the WHO-UMC scale, it was classified as a "Probable ADR." The Naranjo algorithm was also used to calculate the Naranjo score, which was 8, indicating a "Probable ADR" [32]. The Modified Hartwig and Siegel scale was used to measure the severity of this suspected ADR [33]. According to this scale, it was classified as a "Moderate ADR" (level 4 ADR). An ADR form was completed, and the ADR was reported to the nearest Adverse Drug Reaction Monitoring Centre (AMC) under the Pharmacovigilance Programme of India (PvPi) with a unique ID: IN IPC 300668450. The temporal relationship between hypoglycaemia and the administration of levofloxacin, along with the absence of any other concurrently administered drugs as a cause for hypoglycaemia, supports levofloxacin as the cause in our patient. Additionally, our patient had chronic kidney disease, which is frequently associated with fluoroquinolone-induced hypoglycaemia.

This case study highlights the safety concern of hypoglycaemia with levofloxacin use in patients with identified risk factors. Early recognition of this adverse effect and prompt treatment are necessary to prevent morbidity and mortality. Clinicians should exercise caution when prescribing fluoroquinolones and evaluate patients for identified risk factors for hypoglycaemia.

## CONCLUSION(S)

Levofloxacin-induced hypoglycaemia is a rare occurrence; however, it can be severe and persistent, often only responding to the withdrawal of the culprit medication. Unlike most previously reported case reports, this case demonstrates that even patients without a history of diabetes may experience this fatal adverse effect. Clinicians need to be aware of this lesser-known adverse effect to ensure prompt recognition and appropriate treatment. By increasing awareness, we can prevent significant mortality and morbidity associated with this uncommon yet fatal adverse effect.

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