A Rare Case Of Levofloxacin-Induced Fatal Hypoglycemia In A Non-Diabetic Patient With The Review Of Literature

Dr. Yash N. Panchal*, Dr. Bhavesh M. Vyas**

*Third Year Postgraduate Resident, **Associate Professor, Department Of Pharmacology, AMC MET Medical College, Maninagar, Ahmedabad, Gujarat-380008

Abstract: Background: Levofloxacin, a broad-spectrum, third-generation fluoroquinolone antibiotic, is rarely reported to cause life-threatening adverse effects, such as severe hypoglycemia resulting in coma. We report a rare case of hypoglycemia in an elderly non-diabetic patient induced by levofloxacin. A 61-year-old male patient was admitted with severe hypoglycemia. His past medical history revealed treatment with levofloxacin for pneumonia. During his stay in the hospital, the patient was treated with multiple doses of 25 gm 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 stable condition with no clinical symptoms. Clinicians must be aware of this less well-known adverse effect to ensure quick recognition and treatment with the proper adjuncts. [Panchal Y Natl J Integr Res Med, 2023; 14(2): 34-39, Published on Dated: 15/03/2023]

Key Words: Diabetes, Fluoroquinolones, Hypoglycemia, Levofloxacin

Author for correspondence: Dr. Yash N. Panchal, Third Year Postgraduate Resident, Department of Pharmacology, AMC MET Medical College, Maninagar, Ahmedabad, Gujarat-380008, India
E-Mail: dryashpanchal95@gmail.com Mobile: +91-9313737927.

Introduction: Levofloxacin is a broad-spectrum, third-generation fluoroquinolone antibiotic used in the treatment of various bacterial infections[1,2]. With theirhigh oral bioavailability and excellent level of tissue penetration, fluoroquinolones are a widely prescribed class of broad-spectrum antibiotics[3]. Fluoroquinolones are generally consideredsafe antimicrobials with few adverse effects. Although levofloxacin is usually well-tolerated,it may cause life-threatening adverse effects, including severe hypoglycemia resulting in coma[4,5]. Levofloxacin-induced hypoglycemia, however, is a rarely reported adverse effect. Very few cases of levofloxacin-induced hypoglycemia have been reported till now.

The exact mechanism of this adverse effect is unknown but is postulated to be a result of blockage of adenosine 5'-triphosphate-sensitive potassium channels in pancreatic beta-cell membranes6. There are no specific therapeutic options available currently to treat this adverse effect. Here, we report a rare case of life-threatening and refractory hypoglycemia in an elderly non-diabetic patient induced bylevofloxacin.

Case Report: A 61-year-old male patient with amedical history of chronic kidney disease and hypertensionwas presented to the outpatient department of our hospital with the symptoms of headache, dizziness, sweating, anxiety, and confusion from the last two days. On general examination, the patient was in a mild stupor state. His blood pressure was 152/94 mm Hg, while all other vitals were within normal limits. Elementary and cardiorespiratory system examinations did not reveal any abnormality. On examination, the patient was found to be hypoglycemic with a blood glucose level of 40 mg/dL.

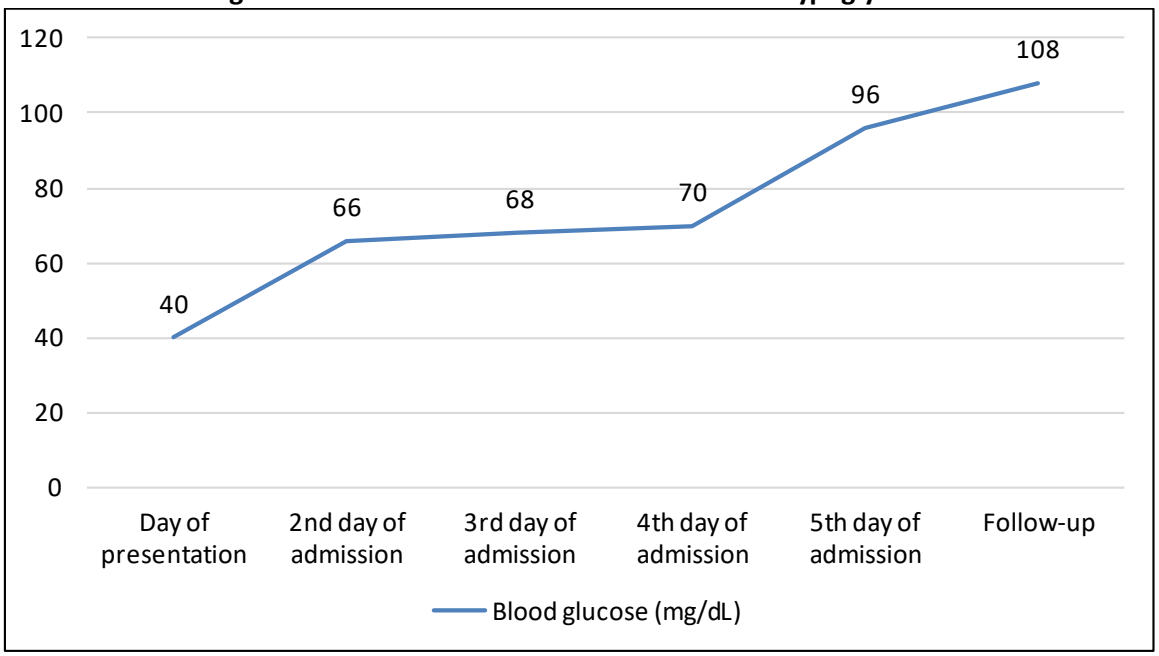
The patient was immediately administered 25 gm dextrose 50% (D50) intravenously, which resulted in the improvement of his mental status. But the patient was still hypoglycemic with a blood glucose level of 62 mg/dL. As a result, the patient wasadmitted to the hospital.

His family history was insignificant. His past medical history revealed admission to some hospital two weeksbefore,with symptoms of worsening dyspnea, cough, fever, and fatigue. He was diagnosed with pneumonia and acute renal failure (Serum creatinine level of 3.96 mg/dL).

He was treated with corticosteroids, diuretics, and levofloxacin. On discharge,the patient was prescribedthe oral levofloxacin 500 mg once daily. The patient was taking levofloxacin regularly for the last five days before presentation to our hospital. Other medications

history revealed regular intake of losartan 50 mg daily, and spironolactone 25 mg daily.The initial laboratory workup revealed hypokalemia with a serum potassium level of 2.7 mEq/L (Normal range: 3.5-5.0 mEq/L), serum sodium level of 138 mEq/L (Normal range: 135-145 mEq/L), albumin level of 2.2 g/dL (Normal range: 3.5-5.0 g/dL), and hypoglycemia with blood glucose level of 66 mg/dL (Normal range: 70-100 mg/dL). Levofloxacin was discontinued. The patient was administered 2 doses of 1 mg glucagon, four boluses of dextrose 50%, and a continuous infusion of dextrose 10% (D10) in the next 2 days due to persistent hypoglycemia. On the fourth day, the patient continued to receive the infusion of D10. The patient's glycemic values returned to the baseline after four days (Blood glucose level of 96 mg/dL on the fifth day)[Figure 1]. The patient was ultimately discharged on the sixth day in stable condition with no clinical symptoms.The patient was instructed to come for a follow-up after one week. During follow-up, the patient was in stable condition, with no active clinical symptoms and his glycemic values were within normal limits (Blood glucose level of 108 mg/dL).

Figure 1: Blood Glucose Trend Of Patient With Hypoglycemia



Discussion: In the differential diagnosis of hypoglycemia, drugs should always be considered. Fluoroquinolones - induced hypoglycemia is a rare butknown fatal adverse effect. Levofloxacin has beennamed as the cause of hypoglycemia in several published case reports[7,8,9,10]. In a few of these cases, delays in identifying the cause of hypoglycemia resulted in unfavourable outcomes. Our case report adds to this emerging data documenting levofloxacin as a cause of hypoglycemia.

While being treated with levofloxacin, somerisk factors may predispose the patient to develop hypoglycemia, such as concurrent use of insulin or sulfonylureas, elderly patient, and renal insufficiency[11,12]. Our patient had no diabetes and wasn't taking insulin or any other oral hypoglycemic medications but was suffering from chronic kidney disease. Several articles have linked the alterations inglucose metabolism with the administration of fluoroquinolones, particularly gatifloxacin[13]. Contrary to other quinolones, there are norandomized controlled trials evaluating the incidence of levofloxacin-induced hypoglycemia. A retrospective, comparative study to evaluate the dysglycemia in the patients receiving levofloxacin, gatifloxacin, ciprofloxacin, or ceftriaxone by Mohr et al. showed that the probability of developing hypoglycemia is greater with levofloxacin (OR, 1.5; 95% CI, 1.2–2.0) and gatifloxacin (OR, 4.3; 95% CI, 2.9–6.3) than with macrolides[14].

The mechanism behind fluoroquinolones-induced hypoglycemia has not still been fully elucidated.

However, studies using the animal model have provided some evidence of the pharmacodynamic pathways that are thought to control insulin secretion[3]. These studies provide explanations for this clinical condition besides 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 causinginsulin release to maintain euglycemia[15,16]. As per in vitro studies, fluoroquinolones block theseATP-sensitive potassium channels, causing the membrane to depolarize, leading to calcium influx through voltage-gated calcium channels and boosting insulin secretion[17,18].

In a mouse model, this effect has been demonstrated[19]. When sulfonylureas bind totheir receptors (Sulfonylurea receptor 1 subunit) located on these KATP channels, these similar molecular events take place. As a result, the same downstream signaling is triggered, and calcium signaling causes the exocytosis of insulin secretory granules[20]. At a cellular level, a total of eight subunits (four SUR1 and four Kir6.2) make up the KATP channels of the pancreatic β-cell[21].

In his study, Saraya et al. found that gatifloxacin, levofloxacin, and temafloxacin inhibit particularly Kir6.2 subunits of these channels of the pancreatic β-cells[18]. Compared to levofloxacin, gatifloxacin, and temafloxacin have more inhibitory potential on the Kir6.2 subuni[22]. This explains why the majority of cases of fluoroquinolones-induced hypoglycemia have been reported with gatifloxacin and not levofloxacin.

Further studies are required to understand any potential unidentified biochemical trigger variables because risks of hypoglycemia 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 reduction in blood glucose levels causes the pancreas to reduce the secretion of insulin and increasingly cogenolysis in the liver. Patients, who are malnourished, such as elderly people, may not have enough glycogen reserves to mobilize in regard to the hypoglycemia induced by fluoroquinolones[24].

This inability to compensate adequately and declining renal functions in elderly people may cause a decrease clearance of drugs in them. This explains why elderly people are more frequently reported to have hypoglycemia caused by fluoroquinolones. Even though levofloxacin was dosed appropriately for pneumonia, our patient did have risk factors (elderly with acute renal failure). This might have caused an accumulation of levofloxacin because of reduced renal clearance and a more prominent dose-dependent pharmaco-dynamic effect.

In our patient, hypoglycemia was documented within 72 hours of levofloxacin administration. Whilethis duration was 24-48 hours in most published case reports of hypoglycemia induced by levofloxacin[25].

In the current case, the course of administration of levofloxacin coincided with the episode of hypoglycemia that was fatal (refractory hypoglycemia with neurological manifestations), and the condition resolved after discontinuation of levofloxacin and treatment with dextrose and glucagon.

Drugs administered concurrently should also be evaluated for their potential to cause a hypoglycemic episode. Our patient was already on losartan and spironolactone due to co-morbidities. However, these drugs are not documented to cause hypoglycemic episodes when given separately or as a potential drug-drug interaction.

There are no specific treatments to reverse the hypoglycemia induced by fluoroquinolones.

Although supportive care treatments such as administration of dextrose and glucagon are the cornerstone of treatment.

Transiently beneficial elevations in serum glucose are offset in this treatment approach by rebound hypoglycemia, which can occur in patients taking drugs like sulfonylureas that affect the pancreatic β-cell KATP channels.

Rebound hypoglycemia particularly occurs in patients with intact pancreatic functionby the additional glucose, stimulatingfurtherinsulin release[26,27].

This phenomenon of rebound hypoglycemia may also occur with fluoroquinolones, given the biological mechanism's similarity to sulfonylureas. Octreotide has been used successfully as a treatment option in some

previously reported cases of fluoroquinolones-induced hypoglycemia[3,28]. Octreotide is a potent and synthetic analog of somatostatin (Inhibitory peptide hormone)[26]. Voltage-gated calcium channels on β cells of the pancreas are coupled to G-protein somatostatin-2 receptors.

The voltage-gated calcium channels remain closed when octreotide binds to these receptors, inhibiting calcium influx into the cell, thus preventing the release of insulin. This mechanism operates downstream of the KATP channel, blocking the sulfonylurea and fluoroquinolone-induced cascade of molecular signalling.

In a questionnaire survey of clinicians conducted by Singh et al. to evaluate the awareness of clinicians towards the hypoglycemic adverse effects of levofloxacin and gatifloxacin, it was found that nearly 80.4% of the participants were unaware that levofloxacin could cause hypoglycemia[13].

This shows that althoughlevofloxacin is a frequently used antibiotic; the awareness of clinicians towards the potential hypoglycemic effect of levofloxacin is poor.

It is imperative to raise awareness about the hypoglycemia induced by levofloxacinto prevent consequent unfortunate consequences. Clinicians should be aware of the risk factors for this adverse effect, as hypoglycemia has the potential to cause major morbidity and mortality. They should alsoincrease monitoring or select an alternate treatment[29].

The re-challenge study was not done with levofloxacin in our patient. World Health Organization-Uppsala Monitoring Centre (WHO-UMC) scale was used for the causality assessment of this suspected adverse drug reaction (ADR).According to the WHO-UMC scale; it was “Probable ADR”.

Using the Naranjo algorithm, the Naranjo score was also calculated. The calculated score was 8, indicating a “Probable ADR”[30].Modified Hartwig and Siegel scale was used to measure the severity of this suspected ADR[31]. According to that, it was “Moderate ADR” (level 4 ADR).

ADR form was filled up, and ADR was reported to the nearest adverse drug reaction monitoring center (AMC) under the Pharmacovigilance Programme of India (PvPi) with a unique ID: IN IPC 300668450. The temporal relationship between hypoglycemia and the administration of levofloxacin and the absence of any other concurrently administered drugs being a cause for hypoglycemia support levofloxacin as the cause in our patient.

Our patient was also suffering from chronic kidney disease, which is frequently cited for fluoroquinolones-induced hypoglycemia.

The safety concern ofhypoglycemia with levofloxacin use in patients with identified risk factors is highlighted by our case study.

To preventmorbidity and mortality,early recognition of this adverse effect and subsequenttreatment are necessary.

Clinicians should be cautious while prescribing fluoroquinolones. They should evaluate patients for identified risk factors for hypoglycemia.

Conclusion: Levofloxacin-induced hypoglycemia is a rare occurrence, although it can be severe and persistent and may responds only to the withdrawal of culprit medication. In contrast to the majority of the previously reported case reports, our case shows that even patients without a history of diabetes may manifest this fatal adverse effect.

Clinicians must be aware of this less well-known adverse effect to ensure quick recognition and treatment with the proper adjuncts. By raising awareness, significant mortality and morbidity associated with this uncommon but fatal adverse effect can be avoided.

Acknowledgement: We would like to thank the patient for allowing us to publish this case report.

References:

1. Thaden JT, Pogue JM, Kaye KS. Role of newer and re-emerging older agents in the treatment of infections caused by carbapenem-resistant Enterobacteriaceae. Virulence. 2017 May 19; 8(4):403-16.
2. Majda A, Rostoff P, Nessler J, Gajos G. Levofloxacin-induced life-threatening hypoglycemia in a type 2 diabetic patient with ST-segment elevation myocardial infarction and community-acquired pneumonia. Clinical Diabetology. 2020; 9(2):141-3.

3. Watson MR, Ward CT, Prabhakar A, Fiza B, Moll V. Successful use of octreotide therapy for refractory levofloxacin-induced hypoglycemia: A case report and literature review. Case Reports in Critical Care. 2019 May 9; 2019.
4. Kelesidis T, Canseco E. Levofloxacin-induced hypoglycemia: a rare but life-threatening side effect of a widely used antibiotic. The American journal of medicine. 2009 Mar 1; 122(3): e3-4.
5. Garber SM, Pound MW, Miller SM. Hypoglycemia associated with the use of levofloxacin. American Journal of Health-System Pharmacy. 2009 Jun 1; 66(11):1014-9.
6. Tomita T, Onishi M, Sato E, Kimura Y, Kihira K. Gatifloxacin induces augmented insulin release and intracellular insulin depletion of pancreatic islet cells. Biological and Pharmaceutical Bulletin. 2007; 30(4):644-7.
7. Fusco S, Reitano F, Gambadoro N, Previti M, Russo G, Basile G, Cucinotta D. Severe hypoglycemia associated with levofloxacin in a healthy older woman. Journal of the American Geriatrics Society. 2013 Sep; 61(9):1637-8.
8. Parra-Riffo H, Lemus-Peñaloza J. Severe levofloxacin-induced hypoglycaemia: a case report and literature review. Nefrología (English Edition). 2012 Jul 1; 32(4):546-7.
9. Lawrence KR, Adra M, Keir C. Hypoglycemia-induced anoxic brain injury possibly associated with levofloxacin. Journal of Infection. 2006 Jun 1; 52(6): e177-80.
10. Micheli L, Sbrilli M, Nencini C. Severe hypoglycemia associated with levofloxacin in Type 2 diabetic patients receiving polytherapy: two case reports. International journal of clinical pharmacology and therapeutics. 2012 Apr 1; 50(4):302-6.
11. Parekh TM, Raji M, Lin YL, Tan A, Kuo YF, Goodwin JS. Hypoglycemia after antimicrobial drug prescription for older patients using sulfonylureas. JAMA internal medicine. 2014 Oct 1; 174(10):1605-12.
12. LaPlante KL, Mersfelder TL, Ward KE, Quilliam BJ. Prevalence of and risk factors for dysglycemia in patients receiving gatifloxacin and levofloxacin in an outpatient setting. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2008 Jan; 28(1):82-9.
13. Singh N, Jacob JJ. Levofloxacin and hypoglycemia. Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America. 2008 Apr 1;46(7):1127-1127.
14. Mohr JF, McKinnon PS, Peymann PJ, Kenton I, Septimus E, Okhuysen PC. A retrospective, comparative evaluation of dysglycemias in hospitalized patients receiving gatifloxacin, levofloxacin, ciprofloxacin, or ceftriaxone. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2005 Oct; 25(10):1303-9.
15. Koster JC, Permutt MA, Nichols CG. Diabetes and insulin secretion: the ATP-sensitive K+ channel (KATP) connection. Diabetes. 2005 Nov 1; 54(11):3065-72.
16. Gloyn AL, Pearson ER, Antcliff JF, Proks P, Bruining GJ, Slingerland AS, Howard N, Srinivasan S, Silva JM, Molnes J, Edghill EL. Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6. 2 and permanent neonatal diabetes. New England Journal of Medicine. 2004 Apr 29; 350(18):1838-49.
17. Maeda N, Tamagawa T, Niki I, Miura H, Ozawa K, Watanabe G, Nonogaki K, Uemura K, Iguchi A. Increase in insulin release from rat pancreatic islets by quinolone antibiotics. British journal of pharmacology. 1996 Jan; 117(2):372.
18. Saraya A, Yokokura M, Gonoi T, Seino S. Effects of fluoroquinolones on insulin secretion and β-cell ATP-sensitive K+ channels. European journal of pharmacology. 2004 Aug 16; 497(1):111-7.
19. Yamada C, Nagashima K, Takahashi A, Ueno H, Kawasaki Y, Yamada Y, Seino Y, Inagaki N. Gatifloxacin acutely stimulates insulin secretion and chronically suppresses insulin biosynthesis. European journal of pharmacology. 2006 Dec 28; 553(1-3):67-72.
20. Sola D, Rossi L, Schianca GP, Maffioli P, Bigliocca M, Mella R, Corlianò F, Fra GP, Bartoli E, Derosa G. State of the art paper sulfonylureas and their use in clinical practice. Archives of Medical Science. 2015 Aug 10; 11(4):840-8.
21. Inagaki N, Gonoi T, Seino S. Subunit stoichiometry of the pancreatic β-cell ATP-sensitive K+ channel. FEBS letters. 1997 Jun 9; 409(2):232-6.
22. Zünkler BJ, Claaßen S, Wos-Maganga M, Rustenbeck I, Holzgrabe U. Effects of fluoroquinolones on HERG channels and on pancreatic β-cell ATP-sensitive K+ channels. Toxicology. 2006 Dec 7; 228(2-3):239-48.

23. Ghaly H, Kriete C, Sahin S, Pflöger A, Holzgrabe U, Zünkler BJ, Rustenbeck I. The insulinotropic effect of fluoroquinolones. Biochemical pharmacology. 2009 Mar 15; 77(6):1040-52.
24. Gupta V SP. Diabetes in elderly patients. JK-Practitioner. 2002; 91:258–9.
25. Patel N, Bindra RS, Modi N, Desai S. Levofloxacin induced hypoglycemia in a non-diabetic patient. 2013; 2(4).
26. Lheureux PE, Zahir S, Penaloza A, Gris M. Bench-to-bedside review: antidotal treatment of sulfonylurea-induced hypoglycaemia with octreotide. Critical Care. 2005 Dec; 9(6):1-7.
27. Dougherty PP, Klein-Schwartz W. Octreotide's role in the management of sulfonylurea-induced hypoglycemia. Journal of Medical Toxicology. 2010 Jun; 6(2):199-206.
28. Klein-Schwartz W, Stassinos GL, Isbister GK. Treatment of sulfonylurea and insulin overdose. British Journal of Clinical Pharmacology. 2016; 81(3):496–504.
29. Morales J, Schneider D. Hypoglycemia. The American journal of medicine. 2014 Oct 1; 127(10): S17-24.
30. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clinical Pharmacology and Therapeutics. 1981; 30(2):239–45.
31. Hartwig SC, Siegel J SP. Preventability and severity assessment in reporting adverse drug reactions. American journal of hospital pharmacy. 1992; 49(9):2229–32.

Conflict of interest: None
Funding: None
Cite this Article as: Panchal Y, Vyas B. A Rare Case Of Levofloxacin-Induced Fatal Hypoglycemia In A Non-Diabetic Patient With The Review Of Literatur. Natl J Integr Res Med 2023; Vol.14(2): 34-39