

## LEVOFLOXACIN INDUCED HYPOGLYCEMIA IN A NON-DIABETIC PATIENT

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### ABSTRACT

Fluoroquinolones are generally regarded as safe antimicrobial agents with relatively few adverse effects or drug interactions. Because of their recognized safety profile and potent in vitro activity, fluoroquinolones have been widely used for the treatment of community- and hospital-acquired infections. Although uncommon, both hypoglycaemia and hyperglycaemia (dysglycaemia) appear to occur with all the fluoroquinolones. It is usually reported in conjunction with impaired creatinine clearance and elderly diabetics receiving concomitant treatment with antidiabetic agents (especially sulfonylureas) or insulin. The exact mechanism of this effect is unknown but is postulated to be a result of blockage of adenosine 5'-triphosphate-sensitive potassium channels in pancreatic cell membranes. Here we report a case of hypoglycaemia in a hospitalized non-diabetic elderly patient in whom this life-threatening adverse effect was related in a temporal fashion to the administration of intravenous levofloxacin meant to cover pulmonary infection in a setting of subacute small bowel obstruction and septicaemia. This case emphasizes the occurrence of profound and prolonged hypoglycaemia consequent upon levofloxacin use, an adverse reaction that has been described with almost all members of the quinolone family of antibiotics. Taking into consideration the frequency of fluoroquinolones use in the hospital and ambulatory setting, clinicians should be cognizant of this potential adverse effect in non-diabetic patients treated with levofloxacin, and they should look out for symptoms of hypoglycaemia and monitor blood glucose levels more frequently, especially early in the course of therapy.

**Key-Words:** Hypoglycaemia; Fluoroquinolones; Levofloxacin

### Introduction

Fluoroquinolones are generally regarded as safe antimicrobial agents with relatively few adverse effects or drug interactions. Because of their recognized safety profile and potent in vitro activity, fluoroquinolones have been widely used for the treatment of community- and hospital-acquired infections. Although uncommon both hypoglycaemia and hyperglycaemia (dysglycaemia) appear to occur with all fluoroquinolones. The weight of the evidence tends to show a higher rate of hypoglycaemia with gatifloxacin than with levofloxacin or ciprofloxacin, the other fluoroquinolones most commonly associated with hypoglycaemia. In United States, Gatifloxacin was voluntarily withdrawn from the market by the manufacturer in 2006<sup>[1]</sup>, just as temafloxacin and clinafloxacin were withdrawn in the 1990s, due to numerous adverse drug events, including hypoglycaemia<sup>[2]</sup>.

Hypoglycaemia typically occurs within the first 3 days of fluoroquinolones therapy and has been

reported after the first dose of either intravenous or oral administration.<sup>[3]</sup> It is usually reported in conjunction with impaired creatinine clearance and elderly diabetics receiving concomitant treatment with antidiabetic agents (especially sulfonylureas) or insulin.<sup>[4]</sup> Measured blood glucose levels as low as 35 mg/dl were reported in Levofloxacin's new drug application.<sup>[5]</sup>

The exact frequency of hypoglycemia associated with the fluoroquinolones is not known. A large phase IV post marketing trial with gatifloxacin (The Tequin Clinical Experience Study) reported an overall frequency of 0.08% (12 of 15,625 patients), although the frequency was higher in patients with diabetes (0.55%) than without diabetes (0.04%).<sup>[6]</sup> Whether the higher frequency in patients with diabetes was due to gatifloxacin administration or the presence of diabetes is not known. Another phase IV study in adult patients receiving levofloxacin for treatment of community acquired pneumonia reported that hypoglycemia, as a serious adverse event, occurred in only two out of 1701 patients (0.1%).<sup>[7]</sup>

Here we report a case of hypoglycaemia in a hospitalized non-diabetic elderly patient in whom this life-threatening adverse effect was related in a temporal fashion to the administration of intravenous levofloxacin meant to cover pulmonary infection in a setting of subacute small bowel obstruction and septicaemia.

## Case Report

A 50 year old woman was brought to the female surgical ward of a tertiary care rural teaching hospital in the afternoon on 24 August 2011 with complaints of abdominal pain, vomiting, diarrhoea, for previous 10 days, accompanied by fever for previous five days. The patient had no previous significant medical history. Correlating with her clinical examination, blood investigations, CT scan and USG of abdomen and pelvis a diagnosis of gall bladder calculi with subacute small bowel obstruction in septicaemia and coagulopathy was made. On admission her blood sugar levels were within normal limits and serum creatinine concentration was 2.4 mg/dl which depicted renal insufficiency. She was kept nil by oral route and intravenous medications were started which comprised of antibiotics (piperacillin 4g + tazobactam 500 mg combination, metronidazole 500 mg, amikacin 500 mg), tramadol 50 mg, pantoprazole 40 mg, ondansetron 4mg, vitamin K and furosemide 40 mg along with intravenous fluids (DNS, RL and Isolyte M). **On day 2**, her chest X-ray revealed consolidation in lung bases, bilateral pleural effusion and cardiomegaly. She was also suspected of having pulmonary tuberculosis. Amikacin was withheld while continuing other treatment. **On day 3**, Anti tubercular treatment (AKT-4) was started along with other medications. Patient's Random Blood Sugar (RBS) values were found to be within normal limits for the first three days of treatment. **On day 4**, Intravenous levofloxacin 500 mg, once daily was started at 6:00AM in the surgical ward to cover pulmonary infection. After 2-3 hours of administration of levofloxacin, patient complained of giddiness and gabbhraman. Patient's RBS was found to be 46 mg/dl at that time, IV dextrose 25% in 100 ml was immediately started for the hypoglycaemic episode. **On day 5**, while continuing same treatment, consistent

hypoglycaemia was noted in the range of 33-57mg/dl for which dextrose 25% was administered along with other intravenous fluids. In the morning of **day 6**, patient complained of giddiness and showed altered sensorium, her blood sugar level was found to be 26 mg/dl. Intravenous dextrose 25% was given stat for the hypoglycaemic episode and the patient was shifted to medical intensive care unit (MICU). In MICU, her RBS was regularly monitored; anti tubercular treatment was put on hold and the rest of treatment was continued. **On day 7**, intravenous levofloxacin was put on hold and monitoring of RBS was done regularly which revealed sugar levels between 22-70mg/dl while continuing other treatment and intravenous fluids. **Till day 8**, episodes of hypoglycaemia/ (dysglycaemia) were noted and dextrose 25% was given regularly. **From day 9, 10, 11**, the patient's RBS came within normal limits while dextrose 25% was given along with other treatment. **From day 12**, Dextrose 25% was put on hold and no further episodes of hypoglycaemia/ (dysglycaemia) were noted till discharge.

## Discussion

The proposed mechanism by which the fluoroquinolones induce glycaemic abnormalities is not clearly understood. Augmentation of insulin release from the islet cells of the pancreas has been reported as the most likely mechanism for fluoroquinolones-induced hypoglycaemia.<sup>[8,9]</sup> Adenosine triphosphate (ATP)-sensitive potassium channels are involved in insulin secretion. When these channels are blocked, the membrane of the  $\beta$ -cells is depolarized, allowing calcium to enter the cell through the voltage-dependent calcium channels. Insulin granules then exit the  $\beta$ -cells, and blood glucose is reduced. The ATP-sensitive potassium channels of the islet cells are inhibited by the fluoroquinolones. Due to this inhibition, insulin secretion is increased, and hypoglycaemia can ensue.<sup>[8]</sup> On a cellular level, eight subunits (four Kir6.2 and four SUR1) comprise the ATP-sensitive potassium channel of the pancreatic  $\beta$ -cell. Saraya et al.<sup>[8]</sup> found that levofloxacin, gatifloxacin, and temafloxacin inhibit the Kir6.2 subunits of pancreatic  $\beta$ -cells. Gatifloxacin and temafloxacin appeared to have greater inhibitory potential than did levofloxacin

on the Kir6.2 subunit, which may explain why more cases of hypoglycaemia have been reported with gatifloxacin than with levofloxacin.

Our patient did not have diabetes and was not receiving insulin or oral hypoglycaemic agents. Consistent with most published case reports, the hypoglycaemia in our patient was documented within 24 hours of levofloxacin administration, and intravenous dextrose was required. The temporal course of hypoglycaemic episodes coincided with intravenous levofloxacin administration, and the condition resolved within a few days of stopping the medication. Hypoglycaemia was severe (i.e., leading to neurologic manifestations and requiring active emergency intervention) and persistent.

Concurrently administered drugs should be considered for their potential to cause hypoglycaemia alone or as a result of a drug-drug interaction. However, concurrently administered sulfonylureas in diabetic patients and antimalarial like quinine & related drugs may augment the hypoglycaemic response of fluoroquinolones due to structural similarity of these agents. In our case, the other drugs given have not been documented to cause hypoglycaemia when given alone or as a drug-drug interaction.

Under normal conditions, the body can compensate for a decrease in blood glucose levels through physiological compensatory mechanisms.<sup>[10]</sup> Normally, a decrease in blood glucose levels causes the pancreas to decrease its insulin secretion and glycogenolysis to increase in the liver. Glucose is produced endogenously from lactate, glycerol, and amino acids.<sup>[11]</sup> Malnourished patients, such as the elderly, may not have sufficient glycogen reserves to mobilize in response to the hypoglycaemia caused by fluoroquinolones.<sup>[12]</sup> This inability to appropriately compensate, along with decreases in renal function in elderly patients, may cause higher drug levels or decreased drug clearance. This may explain why fluoroquinolones-induced hypoglycaemia is most frequently described in older patients.

The association between levofloxacin and hypoglycaemia was evaluated using World Health

Organisation (WHO) Uppsala Monitoring Centre (UMC) Causality Assessment criteria<sup>[13]</sup> Naranjo's Probability Scale<sup>[14]</sup> and Hartwig Severity Scale<sup>[15]</sup>. WHO-UMC scale indicated a probable association. Naranjo's scale revealed a score of +6, signifying a probable association. According to Hartwig severity scale the ADR was placed as level 3. The temporal relationship between levofloxacin administration and hypoglycaemia and the fact that no other co administered drugs being a cause for hypoglycaemia, support levofloxacin as the primary cause in this case. Our patient had a risk factor of renal insufficiency which is often cited for fluoroquinolones-induced hypoglycaemia. Her age may have also been a contributing risk factor.

## Conclusion

This case emphasizes the occurrence of profound and prolonged hypoglycaemia consequent upon levofloxacin use, an adverse reaction that has been described with almost all members of the quinolone family of antibiotics. As compared to most of the previous reports, our case study illustrates that even patients without a history of diabetes or oral hypoglycaemic agent use, can manifest this life-threatening side-effect. Taking into consideration the frequency of fluoroquinolones use in the hospital and ambulatory setting, clinicians should be cognizant of this potential adverse effect in non-diabetic patients treated with levofloxacin, and they should look out for symptoms of hypoglycaemia and monitor blood glucose levels more frequently, especially early in the course of therapy.

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