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WORD COUNT	1894	TIME SUBMITTED	21-FEB-2023 05:23PM
		PAPER ID	96846018

Name of Journal: *World Journal of Pharmacology*
Manuscript NO: 81684
Manuscript Type: CASE REPORT

Recurrent ciprofloxacin induced hypoglycemia in a non-diabetic patient: A case report

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Abstract

BACKGROUND

Fluoroquinolones are a widely prescribed class of broad-spectrum antimicrobials used for various bacterial infections. Frequent use of fluoroquinolones has been questioned due to associated serious adverse effects, including dysglycemia (hypoglycemia or hyperglycemia) due to an alternation in glucose metabolism. Recent clinical trials showed the association of poor clinical outcomes with hypoglycemia in critically ill patients without diabetes. Many predisposing factors worsen fluoroquinolone-induced hypoglycemia, including diabetes, concomitant use of sulfonylureas or insulin, renal insufficiency, and the elderly.

CASE SUMMARY

We report a case of recurrent hypoglycemia after ciprofloxacin initiation for a 71-year-old, non-diabetic, critically ill patient despite the presence of Total parenteral nutrition and Nasogastric tube feeding. The adverse drug reaction probability (Naranjo) scale was completed with a probable adverse drug reaction. The hypoglycemia resolved entirely after ciprofloxacin discontinuation.

CONCLUSION

Ciprofloxacin-induced hypoglycemia is rare. Especial consideration is needed for the elderly due to their higher susceptibility to adverse side effects.

INTRODUCTION

Fluoroquinolones are a commonly prescribed class of broad-spectrum antimicrobials used for various bacterial infections, especially for the treatment of community-acquired pneumonia, as well as intraabdominal and urinary tract infections. Fluoroquinolones exhibit bacteriostatic activity by inhibiting DNA gyrase, the enzyme responsible for replicating Deoxyribonucleic acid (DNA), while their bactericidal activity is achieved by bacterial DNA fragmentation (1).

Routine use of fluoroquinolones has been questioned due to rare but severe associated adverse effects such as heart valve regurgitation, dysglycemia (hypoglycemia or hyperglycemia) due alternations in glucose metabolism, and irreversible side effects affecting the musculoskeletal and nervous systems - most commonly tendonitis and tendon ruptures that can lead to potentially long-lasting disability (2,3,4). Adverse drug events (ADEs) can be life-threatening, particularly in the critically ill population. Patient factors, environmental factors, and drug classes related to ADEs differ in intensive care compared to general care units. Hypoglycemia was associated with increased intensive care unit (ICU) length of stay and increased utilization of mechanical ventilation, catecholamines, and renal replacement therapy (5)

Many predisposing factors are known to increase the incidence of hypoglycemia in patients treated with fluoroquinolones, including diabetes, concomitant use of sulfonylureas or insulin, renal insufficiency, and advanced age (conventionally defined as greater than 65 years old) (6). We report a case of recurrent hypoglycemia in a non-diabetic patient that resolved successfully after ciprofloxacin discontinuation.

CASE PRESENTATION

Chief complaints

Unexplained recurrent hypoglycemia

History of present illness

On the first day following abdominal closure, enteral feeding was initiated through a nasogastric tube (NGT), and the following day total parenteral nutrition (TPN) was initiated to augment his nutritional state. As a result, his blood glucose readings rose and were maintained above 99 mg/dL for the rest of his stay. Furthermore, as the patient tolerated the NGT feeding well, it was gradually increased over the following days.

Due to worsening sepsis and increased vasopressor requirements, 400 mg of ciprofloxacin was administered intravenously (IV) every 12 hrs and adjusted accordingly on day two following surgery, based on a positive culture result. Approximately 30 h later, the patient had an episode of symptomatic hypoglycemia and received 12.5 mg of glucose IV, which somewhat improved his blood glucose level. However, his relatively low blood glucose readings continued despite increasing calories through TPN and NGT feeding. Therefore, Additional dextrose infusion was added to avoid further hypoglycemic episodes. After reviewing all the medications and evaluating his caloric intake during the daily rounds, we suspected that the ciprofloxacin might be the culprit behind the patient's hypoglycemia. Retrospectively, we examined his most recent blood glucose readings and observed a downward trend in his blood glucose readings that started immediately following the second dose of ciprofloxacin. Accordingly, it was discontinued and the antimicrobial strategy was modified.

History of past illness

Our patient was a 71-year-old male who suffered from hypertension, peripheral vascular disease, and dyslipidemia, with a previous history of aortobifemoral bypass

surgery. He was admitted to the hospital following a two-month complaint of abdominal pain. On admission his pain was moderate, and he was hemodynamically stable with a blood glucose concentration of 126 mg/dL, Glasgow Coma Scale/Score (GSC) of 15/15, and unremarkable lab results.

He underwent exploratory laparotomy due to possible bowel ischemia, but only dusky bowel was found with no evidence of perforation or ischemia. His hospital course was complicated, requiring multiple ICU admissions for various reasons including sepsis, septic shock, acute kidney injury (AKI), abdominal fluid collection, and electrolyte imbalances.

One month after his hospital admission, he underwent another exploratory laparotomy due to wound dehiscence and a bowel perforation. Multiple micro-perforations in the small bowel and bowel ischemia were discovered during surgery, the abdomen was kept open, and he required three more surgeries afterward. His final fifth surgery was for abdominal closure.

Personal and family history

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Physical examination

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Laboratory examinations

Multiple glucose blood levels were recorded in correlation to ciprofloxacin administration.

Imaging examinations

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FINAL DIAGNOSIS

Ciprofloxacin induced hypoglycemia

TREATMENT

Increasing calories through TPN and NGT feeding.

Additional dextrose infusion was added as needed to maintain normal blood sugar.

After ruling out other possible causes, ciprofloxacin was discontinued .

OUTCOME AND FOLLOW-UP

After 12 h of ciprofloxacin discontinuation, all his readings were 126 mg/dL, and the dextrose infusion was stopped. 24 h later, and despite decreasing the enteral feeding amount due to a high gastric residual resulting in a significant decrease in his total caloric intake, insulin infusion had to be initiated to control his blood glucose readings.

DISCUSSION

Recent clinical trials have shown a connection between poor clinical outcomes and hypoglycemia in critically ill patients without diabetes, emphasizing the harm caused by severe hypoglycemia and challenging the intensive glycemic control strategy to manage both diabetic and critically ill patients. Although hypoglycemia is uncommon in patients without diabetes, many etiologies can cause hypoglycemia including sepsis, liver diseases, malnutrition, alcohol-related diseases, malignancies, post gastrectomy syndrome, and endocrine disorders. (7)

Fluoroquinolones are antibiotics widely used in the treatment of various bacterial infections, but several adverse effects have been reported with their use. In 2018, The US Food and Drug Administration (FDA) announced new drug safety communications regarding fluoroquinolones and the risk of hypoglycemia. Their reports showed that levofloxacin caused most of the incidents, followed by ciprofloxacin. In the end, the

FDA strengthened the warnings for the prescribing information that fluoroquinolone antibiotics may cause significant decreases in blood sugar and certain mental health side effects (8,9). Many retrospective studies have shown that fluoroquinolones significantly interfere with glucose homeostasis and insulin secretion, leading to hypoglycemia and hyperglycemia events. The pathophysiological mechanism of hypoglycemia associated with fluoroquinolones is not yet fully understood. However, animal and *in vitro* studies hypothesized that fluoroquinolones block adenosine triphosphate-sensitive potassium (KATP) channels in pancreatic □-cells, which in turn leads to an increase in insulin release (10,11,12,13).

Two large retrospective cohort studies by Aspinall *et al* and Mohr *et al* on diabetic outpatients revealed the high risks of hypoglycemia associated with fluoroquinolone treatment. However, the risk of a clinically-relevant dysglycemic event appears to vary highly among this class of drugs, with significantly greater risks for gatifloxacin and levofloxacin compared to ciprofloxacin (14,15). Chou *et al* conducted a retrospective cohort study among 78,433 outpatient diabetic patients for 22 mo; the study results identified an association between fluoroquinolones and a higher risk of hypoglycemia(3). Moxifloxacin was associated with the highest risk of hypoglycemia, followed by levofloxacin, with ciprofloxacin carrying the least risk (16).
Many case reports have documented levofloxacin-induced hypoglycemia in diabetic patients, and one case report detailed fatal hypoglycemia with ciprofloxacin in a diabetic patient with end-stage renal disease due to diabetic neuropathy (13,17,18,19).

A 2019 research article suggested an association between ciprofloxacin and hypoglycemia in patients without diabetes. We conducted a search of the World Health Organization's global adverse drug reaction database using "ciprofloxacin" as the drug substance and "hypoglycemia" as the reaction term. We found a total of 35 cases of hypoglycemia reported since 1989 from 17 countries in patients without diabetes associated with ciprofloxacin use, with a median time-to-onset of four days. The cases

had a median age of 64 years (interquartile range, 50–85) with a balanced male-to-female ratio (but one of the limitations was that hyperinsulinemia or diabetes could not be ruled out) (17).

Our patient's Naranjo Adverse Drug Reaction Probability Scale was six, which indicates a "probable adverse drug reaction". However, the Naranjo score may have limitations in evaluating adverse drug reactions in critically ill patients, such as difficulty re-challenging patients, the inapplicability of placebo administration, possible lack of serum drug concentrations, and clarification of objective measurement.

Hyperglycemia is a known metabolic complication of TPN, due to the presence of dextrose as the primary energy source in TPN ,that commonly occurs in diabetes mellitus or insulin-resistant patients. It can occur in patients without diabetes as well, with risk increasing due to the presence of other risk factors such as age, illness severity, and TPN infusion rate. Hypoglycemia, by contrast typically occurs in cases of excess insulin administration *via* parenteral nutrition solution. Usually, the risk of hypoglycemia increases along with certain patient characteristics (e.g. age), medications, and comorbidities (e.g. diabetes mellitus, mechanical ventilation, renal frailer, sepsis, and nutritional status) (12).

In our case, the patient was euglycemic from his initial hospital admission, despite developing severe sepsis and septic shock several times before that latest encounter without any episodes of hypoglycemia that eliminated the severe illness condition as the sole reason for hypoglycemia. Moreover, during the incident mentioned above, and in response to his low blood glucose readings, our medical team, nutritionist, and clinical pharmacist tried to address the issue by increasing the patient's total caloric intake through various sources, including starting dextrose infusions, maximizing his TPN dose, and diluting all his IV medications in dextrose solutions. The risk of mechanical ventilation and AKI-induced hypoglycemia, as well as other possible

comorbidities, are negligible for this case because these comorbidities did not induce hypoglycemic events before initiating ciprofloxacin. The only risk factor that may have predisposed our patient to hypoglycemia while receiving fluoroquinolone was his advanced age of 71. Renal function decreases as part of the normal aging pathophysiology, even without concomitant renal disease. That results in the accumulation of drugs that depends on renal excretion as the primary eliminated route, like ciprofloxacin. Impaired drug clearances affect the kinetics of drugs in prolonged half-lives, high drug serum concentration and increased side effects and toxicity. (20)

Interestingly, after stopping ciprofloxacin, he started to become hyperglycemic, and although his caloric intake was reduced as a response, he required insulin infusion to achieve proper glycemic control.

The prevalence of ADEs increases with age due to age-related changes in pharmacokinetics and pharmacodynamics, increasing comorbidity burden, and polypharmacy. This makes older patients more sensitive to the side-effects of medications than their younger counterparts. A trained clinician can predict and detect ADEs in vulnerable patients by maintaining detailed documentation and regularly reviewing all prescribed and over-the-counter medications through standardized medication reconciliation. It is also important to outline clear therapeutic goals and recognize various drugs' impacts on multiple organ systems for newly prescribed medications (15).

CONCLUSION

Although hypoglycemia caused by ciprofloxacin is rare, it can cause fatal complications. Therefore, it should be prescribed carefully, after considering the patient's risk factors, especially the geriatric population who are more susceptible to adverse side-effects.

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