CASE REPORT

Severe Cotrimoxazole-induced Hypoglycemia in a Patient with *Pneumocystis jirovecii* Pneumonia: A Case Report

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Abstract

Aim: To report a case of prolonged severe hypoglycemia associated with cotrimoxazole in a nondiabetic human immunodeficiency syndrome (HIV)—positive patient.

Case description: We describe a case of cotrimoxazole-associated hypoglycemia in a 30-year-old nondiabetic HIV-positive patient. The patient developed hypoglycemia after she was started on cotrimoxazole for the treatment of *Pneumocystis jirovecii*. Her renal and hepatic function was normal. Serum insulin and C-peptide measured at the time of hypoglycemia were found to be significantly elevated. Hypoglycemia was managed with intravenous administration of dextrose and resolved after cotrimoxazole was withdrawn. We also review the literature regarding this uncommon adverse effect of the commonly used drug.

Keywords: Cotrimoxazole, Hypoglycemia, *Pneumocystis jirovecii* pneumonia.

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Introduction

Cotrimoxazole (trimethoprim-sulfamethoxazole) is a commonly used antibiotic in wide clinical use. It is the first-line agent for both the treatment and prophylaxis of *Pneumocystis jirovecii* infection in immunosuppressed patients.[1] It is also commonly used in the treatment of urinary and respiratory infections. A number of adverse effects related to cotrimoxazole have been described, ranging from mild gastrointestinal intolerance to hypersensitivity reactions to hematological problems.[2] Hypoglycemia is a rarely seen complication of cotrimoxazole use.[3] We report a case of severe hypoglycemia in an human immunodeficiency syndrome (HIV)—positive patient who was started on cotrimoxazole for the treatment of *Pneumocystis jirovecii* pneumonia. We review the literature and discuss predisposing causes, diagnosis, and management of severe hypoglycemia in this scenario.

Case Description

A 30-year-old HIV-positive patient was admitted with complaints of progressive breathlessness. She had been on a combination of dolutegravir, emtricitabine, and tenofovir alafenamide as part of her anti-retroviral therapy regimen previously. On examination, she appeared malnourished and was dyspneic. Baseline investigations showed normal leukocyte counts, with normal renal and liver function tests. Computed tomography scan of the chest showed ground glass opacities in the perihilar region, raising the possibility of *Pneumocystis* pneumonia in this scenario (Fig. 1).

Treatment was initiated with oral cotrimoxazole (at a dose of two double-strength tablets thrice daily), intravenous methylprednisolone (40 mg twice daily), and oxygen. The patient developed symptoms of giddiness and sweating 2 days after starting cotrimoxazole. The glucometer blood glucose level at this time was found to be 35 mg/dL. The patient did not have any previous history of diabetes or hypoglycemia. Her glycated hemoglobin was 5.8%. She continued to have recurrent hypoglycemia despite correction with boluses of 25% dextrose and continuous infusion of

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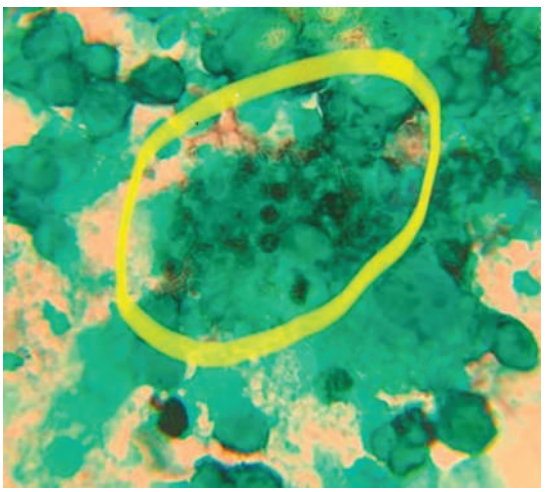

Fig. 1: Grocott's methenamine silver stain showing *Pneumocystis jirovecii*

25% dextrose. Laboratory plasma glucose value at the time was also low. Plasma insulin sent at the time of hypoglycemia was 138 µIU/mL with a C-peptide level of >20 ng/mL (Table 1).

A diagnosis of cotrimoxazole-related hypoglycemia was considered, and cotrimoxazole was discontinued. The diagnosis of *Pneumocystis* pneumonia was confirmed, with BAL being positive for *Pneumocystis jirovecii*. Treatment for *Pneumocystis* pneumonia was continued with clindamycin and primaquine. The severity of hypoglycemic episodes gradually decreased, and intravenous 25% dextrose was gradually tapered and stopped over the next 48 hours. This denotes the onset of hypoglycemia on day 3 after starting cotrimoxazole. After stopping cotrimoxazole, the blood glucose levels showed an improvement from day 5, as plotted on the graph (Fig. 2).

Discussion

Cotrimoxazole has structural similarities to sulphonylurea drugs used in the treatment of type 2 diabetes mellitus. Both are derivatives of sulfanilamide.[4] The sulfa component is postulated to bind to insulin-secreting pancreatic β-cells and stimulate insulin hypersecretion.[5] The findings of elevated insulin and C-peptide seen in our patient, as well as other reported cases, are also evidence of insulin secretion caused by cotrimoxazole.

A 2006 review of 14 cases of cotrimoxazole-related hypoglycemia by Strevel et al. found that insulin levels were elevated by 88%.[3] This review also reported an additional predisposing factor for hypoglycemia, such as impaired renal function, impaired hepatic function, and concomitant use of other drugs, which could cause hypoglycemia in all of these patients. Around 50% of these patients were on more than two double-strength tablets of cotrimoxazole per day.

The mean duration of therapy before the onset of hypoglycemia was 7 days (range 1–18). The time to hypoglycemia in our case was 4 days, with seizure activity noted on day 7. This is consistent with the literature; Strevel et al.[3] concluded that the median time to hypoglycemia in the cases published before 2006 was 7 days.

Since most of the patients using cotrimoxazole do not develop hypoglycemia, we assessed the patient for other predisposing factors. The patient had developed severe hypoglycemia in spite of being on 80 mg per day of methylprednisolone, which could theoretically protect against hypoglycemia. Biochemical investigations, including electrolytes, liver function tests, creatinine, and thyroid profiles, were within normal limits. Poor caloric intake and malnutrition (body mass index of 17 kg/m^2) could have contributed to hypoglycemia. Use of the proton pump inhibitor esomeprazole could have further predisposed to hypoglycemia. Cotrimoxazole-related hypoglycemia may be more common in HIV-positive individuals due to the frequent polypharmacy seen in this subgroup, in addition to the increased prevalence of malnutrition and organ dysfunction.[6]

There are few case reports in the literature of hypoglycemia associated with cotrimoxazole in an HIV-infected patient. In a study conducted by Schattner et al.,[7] while treating a 34-year-old who was infected with HIV with intravenous cotrimoxazole treatment for *Pneumocystis carinii*. The patient had hypoglycemia with a serum glucose level of 19.6 mg/dL. Serum insulin level was 12 mU/L with an increase in C-peptide and cortisol levels 6 days after the administration of cotrimoxazole. The authors propose that there is a strong likelihood of elevated drug concentrations, with hepatitis being a contributing factor. Liver illness may have worsened the hypoglycemia by compromising the processes of glycogenolysis and gluconeogenesis.[7] Hence, it is plausible that inadequate nutritional consumption could have had a role in this particular instance. This notion is substantiated by the presence of elevated levels of insulin and/or C-peptide in numerous case reports[4,6,8] and in our own patients. The incidence of hypoglycemia seems to be dependent on the dosage administered. Two case reports have shown that adjusting the dose of cotrimoxazole based on renal function resulted in the absence of additional symptoms of hypoglycemia.[6,9]

Renal impairment seems to be the strongest risk factor associated with cotrimoxazole-related hypoglycemia. A total of 16 of 21 cases reported had proven renal impairment.[10] An estimated 10–30% of cotrimoxazole is renally excreted; dosage reduction is recommended when the glomerular filtration rate (GFR) is between 15 and 30 mL/minute. Appropriate dose adjustment and cautious use are advised if GFR is <15 mL/minute.[2] The half-life of sulfamethoxazole is 8–14 hours in individuals with normal renal function as compared to 20–50 hours in patients with end-stage renal disease.[11] Reduced renal clearance likely facilitates drug accumulation, with increased drug concentrations leading to sulfonylurea-like actions. Renal impairment is also associated with prolonged duration of hypoglycemia.[8] Prolonged starvation, as well as malnutrition, is also reported to contribute to hypoglycemia.[6,12]

Cotrimoxazole can increase the risk of hypoglycemia in diabetic patients using sulfonylureas or meglitinides.[8,13] Trimethoprim inhibits hepatic *CYP2C8*, and sulfamethoxazole inhibits *CYP2C9*, thus inhibiting the metabolism of sulfonylureas and repaglinide, with a resulting increase in drug levels.[9] A large cohort study by Tan et al., reviewing patients older than 66 years on glipizide or glyburide, reported a significantly higher risk of hypoglycemia in patients coprescribed cotrimoxazole with an odds ratio of 3.78 (1.81–7.9).[14] This highlights the importance of blood glucose monitoring when starting cotrimoxazole in diabetic patients, especially those who are elderly and with multiple comorbidities.

Table 1: Gives the summary of serum insulin levels and C-peptide levels of the patient

Plasma insulin	*138 µIU/mL*
C-peptide level	>20 ng/mL

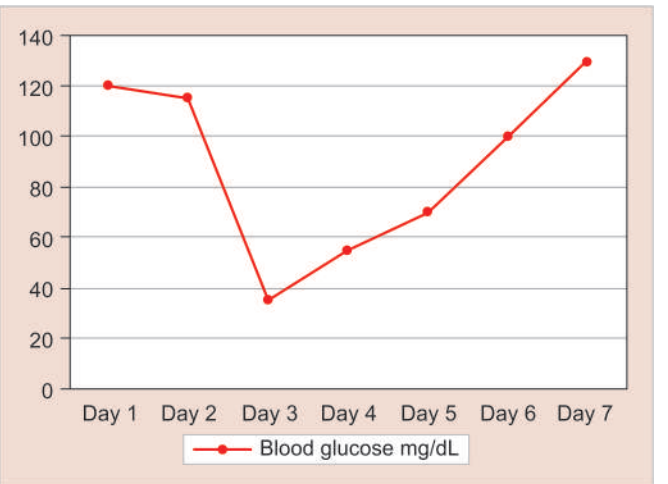

Fig. 2: Represents the average blood glucose levels for each day plotted on the graph

Almost all cases with severe hypoglycemia related to cotrimoxazole required intravenous glucose administration.[3,15] Prolonged hypoglycemia lasting for >12 hours was also reported in a number of cases.[3,8] Drugs such as glucagon, octreotide, and diazoxide have also been used in patients with refractory hypoglycemia.[16,17] Further continuation of cotrimoxazole at a reduced dose has also been possible in a few patients.[5]

Hypoglycemia can present with a broad range of severity, ranging from mild hypoglycemia with only a headache to severe hypoglycemia causing loss of consciousness and seizures. Milder cases of hypoglycemia may be underreported, given the frequency of use of cotrimoxazole. A study by Kenteu et al. aimed to evaluate the effects of prophylactic doses of cotrimoxazole on glucose metabolism in healthy volunteers. Cotrimoxazole was found to induce a 10% reduction in glucose levels in two-thirds of the volunteers within 120 minutes of administration.[18] Clinicians should, therefore, be aware of this potentially serious adverse effect when using cotrimoxazole in susceptible patients.

Conclusion

Cotrimoxazole-induced hypoglycemia is a rare but life-threatening adverse effect that may occur in patients with comorbidities such as renal impairment, diabetes mellitus, hepatic impairment, and malnutrition or HIV infection. The present case report exemplifies the importance of vigilance in monitoring for signs of hypoglycemia after the initiation of high-dose cotrimoxazole therapy, particularly in younger patients lacking previous risk factors such as renal or hepatic dysfunction. In order to mitigate the occurrence of seizures, coma, and fatality, it is imperative to rapidly administer intravenous dextrose. Conducting a thorough assessment of the patient's medication regimen before initiating cotrimoxazole can serve as a preventative measure against the occurrence of hypoglycemia.

Authors' Contributions

- Conceptualization: Dr K Swarna Deepak, Dr Samantha.
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- Formal analysis: Dr K Swarna Deepak, Dr K Hima Bindu.
- Methodology: Dr K Swarna Deepak.
- Project administration: Dr K Swarna Deepak, Dr Samantha.
- Visualization: Dr K Hima Bindu.
- Supervision: Dr K Swarna Deepak.
- Resources: Dr K Swarna Deepak, Dr Samantha.
- Writing of the original draft: Dr K Swarna Deepak, Dr Samantha.
- Review and editing: Dr K Hima Bindu.
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All authors approve the version to be submitted, and all authors agree to be accountable for all aspects of the manuscript.

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