

Case Report

Monday Blues – Rare Cause of Hypoglycemia in a Child with Leukemia

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Abstract

Hypoglycemia in a child with acute lymphoblastic leukemia (ALL) often makes the clinician think of sepsis or metabolic disturbances due to relative adrenal insufficiency with steroid withdrawal. We report a rare scenario of drug-induced hypoglycemia in a child on treatment for ALL. Recurrent symptomatic episodes of hypoglycemia in a 4-year-girl on treatment for high-risk ALL were analyzed and it was surprising to note that the episodes were noted on early hours on Monday and Sunday nights. Detailed evaluation for the etiology and the workup was not contributory. With the background of drug history for ALL maintenance and occurrence of episodes on Mondays, possibility of drug-induced hypoglycemia secondary to cotrimoxazole was considered. Dose alteration for trimethoprim-sulfamethoxazole was considered stopping the drug is not feasible. Malnutrition was attributed as the coexisting risk factor in our child.

Keywords: Acute lymphoblastic leukemia, cotrimoxazole, drug-induced, hypoglycemia, malnutrition

INTRODUCTION

Occurrence of hypoglycemia in a child on treatment for acute lymphoblastic leukemia (ALL) often makes the clinician think of sepsis or metabolic disturbances due to relative adrenal insufficiency with steroid withdrawal. Drug-induced hypoglycemia is a well-known phenomenon, associated commonly with diabetic drugs, beta-blockers, and quinolones.^[1] Trimethoprim-sulfamethoxazole (TMP-SMX) as a cause of hypoglycemia, though has been described earlier, is rarely encountered and considered in clinical practice, in comparison to the wide usage of this drug as pneumocystis carinii pneumonia (PCP) prophylaxis in immunocompromised patients.^[2] Hypoglycemia related to TMP-SMX has been noted in association with renal failure and usually reverses with discontinuation of the drug.^[2] We report a rare scenario of TMP-SMX-induced hypoglycemia in a child on treatment for ALL.

CASE REPORT

Our patient is a 4-year-old girl, diagnosed with high-risk B-ALL and is on treatment chemotherapy for past 1.5 years. Her anthropometry revealed weight for height below-2 Z-score.

She has had two episodes of asymptomatic hypoglycemia during her consolidation chemotherapy which was attributed to probable sepsis related to neutropenia.

While on maintenance protocol, she had three episodes of drowsiness, excessive perspiration, and feeling cold during morning hours while the mother would attempt to awaken the child. There were no episodes of headache, vomiting, seizures, or focal weakness. Blood glucose levels monitored during one such episode were low. Quick clinical recovery was noted once she was fed with milk containing extra sugar and calorie dense ready to eat sweets. These episodes were not associated with any fever or had any detectable focus of infection. Her vitals examined by emergency physicians were stable all throughout except for tachycardia during the episodes.

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Critical sample done during an episode of hypoglycemia revealed mild lactic acidosis, low insulin, and C-peptide levels. The episodes were analyzed and it was strikingly surprising to note the episodes were noted on early hours on Monday twice and at bedtime on Sunday once. With the background of drug history for ALL maintenance (weekly methotrexate and daily 6-mercaptopurine along with TMP-SMX for PCP prophylaxis), possibility of drug-induced hypoglycemia secondary to TMP-SMX was considered. Dose modification was considered as we could not discontinue the drug for lack of a better and economical alternative.

Parents were explained about the calorie dense and frequent feeding to prevent hypoglycemic episodes and with such modifications, child is doing well clinically.

Discussion

TMP-SMX is an integral part of management in all the pediatric malignancies administered for PCP prophylaxis. Bone marrow suppression causing cytopenias is a known adverse effect of the drug, apart from gastrointestinal discomfort, skin rash, Stevens-Johnson syndrome, and transaminitis. Hypoglycemia secondary to TMP-SMX is a rare phenomenon, however, well reported in literature.

The similarity of the structure of the drug, especially the SMX component to sulfonyleureas has been proposed as the mechanism of hypoglycemia in these patients. It binds to the beta-cell receptors in pancreas and increases endogenous insulin secretion. However, not all reported cases of hypoglycemia had hyperinsulinism and elevated C-peptide level, similar to our case.^[1] Possibility of drug interactions with TMP-SMX has been suggested in some patients. SMP selectively inhibits CYP2C9 enzyme and hence, drug interactions need to be carefully looked into.^[3] An irreversible agonism or an autoimmune phenomenon was proposed after observing prolonged hypoglycemia for 47 days following drug discontinuation.^[4]

Main route of excretion of drug is hepatic followed by renal elimination constituting 10%–30% elimination. Among the drug-induced hypoglycemia, TMP-SMX belongs to the class of drugs causing hypoglycemia with very low level of evidence.^[2]

It is interesting to note that, despite sulfonyleureas were developed following discovery of sulfonamide-induced hypoglycemia; the incidence of TMP-SMX-induced hypoglycemia is very less.

Reports of refractory hypoglycemia secondary to the drug in patients with severe diabetes and acquired immunodeficiency syndrome have been described. The risk factors which could predispose to hypoglycemia in certain patients include elderly age group, liver dysfunction or renal failure (delayed clearance), diabetics on oral hypoglycemic agents, malnutrition, and probably, prescribing at a higher dosage.^[1] In our patient, renal and liver functions have been normal and moderate malnutrition was probably the predisposing factor.

Neuroglycopenic symptoms are very severe in elderly and those with renal failure. Dose reduction of the drug has been proposed in a few cases, however, needs more clarity. Although discontinuation of the drug resolves the hypoglycemia, in immunocompromised patients requiring long-term prophylaxis, the risk of PCP infection is a major concern.^[5] Alternative drugs including pentamidine are not easily available, expensive and also have been reported to have similar complication in immunocompromised hosts.^[6] In our patient, we have counseled the parents regarding the phenomenon and also about the need for ongoing prophylaxis. Necessary dose modifications have been suggested and a prebed/nocturnal feed with a high glycemic index diet was advised.

To our best knowledge, similar report in pediatric age group with TMP-SMX-induced hypoglycemia has not been reported. Careful analysis of the symptoms to specific time of the week and correlation to drugs has led to the diagnosis in our patient before the complications ensued. The pediatric oncologists and the pediatrician who share the care during less-intensive phases of chemotherapy should be aware of this entity, though rare, to prevent potential complications with a timely diagnosis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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