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Title

Severe Recurrent Nocturnal Hypoglycemia During Chemotherapy With 6-mercaptopurine in 2 Children With Acute Lymphoblastic Leukemia

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Introduction

Hypoglycemia is diagnosed based on the appearance of symptoms of brain dysfunction and sympathetic system stimulation, both of which are induced by a low serum glucose concentration.1 Hypoglycemia in children receiving
chemotherapy for acute lymphoblastic leukemia (ALL) has many potential causes, including but not limited to liver failure, acute or chronic pancreatitis, and the side effects of drugs (most commonly steroids, asparaginase, and 6MP). Although mild asymptomatic hypoglycemia is a common adverse effect during the early phase of ALL chemotherapy, severe symptomatic hypoglycemic induced by drugs is rare, especially during the maintenance phase.2 Here we present the cases of 2 boys in the maintenance phase of ALL chemotherapy who developed severe symptomatic hypoglycemia, which was especially prominent in the morning. In both patients, the hypoglycemia was attributed to 6MP, given that all other possible causes were excluded. Neither child had a history of glycemic disturbance before or during the initial phase of therapy.

To the best of our knowledge, this is the first report of severe hypoglycemia associated with 6MP in the Arab world, specifically in Oman.

Methodolgy

A)- First Case: A 4-year-old boy was being treated with maintenance
therapy according to the UKALL 2011 protocol (high-risk arm). The treatment consisted of oral administration of (dexamethasone 3 mg/m2 twice daily for 5 days every 4 weeks), monthly vincristine, 6MP (75 mg/m2 per dose daily), and methotrexate (20 mg/m2 weekly). The child complained of episodic low activity and his mood fluctuated between sleepy and anxious, mostly during the morning. However, he experienced neither pain nor distress. He also had no sweating episodes or tremors.

His mother is a staff nurse, and she attributed the recurrent episodes to the weekly dexamethasone treatment and vincristine. Glucose was measured in randomly obtained blood sample and the level was consistent with hypoglycemia (40 to 50 mg/dL). All stress hormones (cortisol, insulin, and growth hormone) and liver function tests were normal, as were the basic metabolic screening tests (blood gas, lactate, and ammonia). Blood sugar measurement before sleep, and dexamethasone administration during themorning and afternoon, were advised. Enrichment of the child's food with complex carbohydrates was also recommended, particularly for the evening meal. Although these measures reduced the severity of symptoms, the patient's mood fluctuations persisted.

Hence, the episodic hypoglycemia was attributed to 6MP, and the mother was therefore advised to administer the drug during the morning instead of at bedtime and to continue giving her son food that was rich in complex carbohydrates.

Follow-up at home and regular clinical visits showed a dramatic improvement in the child's clinical symptoms and no further episodes of low blood sugar B)- second case : A 6-year-old boy with ALL being treated according to the UKALL 2011 protocol was on his third cycle of maintenance therapy (each chemotherapy cycle is 3 months long and includes the same agents reported in Case 1). For several months, coinciding with the start of the maintenance phase, the patient had complained of generalized bony discomfort, fatigue, and cold sweating episodes early in the morning, as reported by his parents. Measurements of blood glucose at these episodes were reported to be ranging from 18 to 50 mg/dL. It required correction with dextrose 10% on 2 occasions as he reported to his local hospital with symptomatic hypoglycemia of 18 mg/dL. His liver function tests were normal, as were his growth hormone, insulin, and ammonia levels, which excluded endocrine and metabolic causes. Secondary hypoglycemia caused by 6MP was thus considered the cause of hypoglycemia. The 6MP administration time was therefore changed to the morning and a carbohydrate-rich meal before bedtime was recommended.

Conclusion

Clinicians should be familiar with the adverse effects of the chemotherapeutic agents administered to ALL patients and how to manage them. 6MP can induce hypoglycemia during the maintenance phase, especially in very young patients, who should thus be carefully monitored. Effective management consists of changing the time of 6MP administration or temporarily withholding the drug. Further studies on the mechanism of 6MP-induced hypoglycemia and its optimal treatment are necessary.