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Intractable Feeding Intolerance and Abdominal Distention in a Preterm Infant: An Unusual Side Effect of Diazoxide

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Abstract

Hyperinsulinemic hypoglycemia (HH) is the most common cause of persistent hypoglycemia in infants. The first choice of medical treatment for HH is diazoxide, sodium and fluid retention being commonly associated its side effects. Other cardiovascular and hematological adverse effects have also been reported. Presented herein is case of a preterm infant (gestational age: 31 weeks) with HH who developed severe feeding intolerance and abdominal distention following diazoxide treatment. After structural and functional gastrointestinal disorders have been excluded symptoms resolved completely after discontinuation of the drug. To the best of our knowledge, this is the first report of such an unusual association which we believe deserves special consideration during the follow-up of infants under treatment with diazoxide.

Keywords: Diazoxide; Hyperinsulinemic hypoglycemia; Side effect; Feeding intolerance; Abdominal distention

Introduction

Hyperinsulinemic hypoglycemia (HH) is a term used to describe the state of uncontrolled secretion of insulin despite the presence hypoglycemia. HH is the most common cause of persistent hypoglycemia in infancy.1 Clinical manifestations of HH in the neonatal period range from mild to very severe, resulting in unresponsive hypoglycemia [1]. Being attentively for diagnosis and treatment is necessary to avoid neurologic damage from recurrent or prolonged episodes of hypoglycemia. Basic treatment of HH includes parenteral administration of glucose as well as adhering to a consistent frequent feeding schedule. Several medications have been used in the management of HH. Diazoxide is a thiazide drug (potassium channel activator) that is recommended as first line medical therapy for this condition [1] and exhibits a vasodilator effect which makes it a useful option for the treatment of acute or malignant hypertension. Reported adverse effects include inhibition of insulin secretion from the pancreas, sodium and fluid retention, cardiac failure and pulmonary hypertension due to direct toxic vascular injury, hyperuricemia, leukopenia, and neutropenia [2,3]. Incidentally, the drug's effect on insulin secretion has made it an attractive first-line option for the treatment of HH. Other medications that have also been suggested include octreatide and nefedipine. Furthermore, intravenous glucagon has been proven to be helpful in stabilizing blood sugar levels prior to subtotal pancreatectomy surgery [2,3].

Presented here is a case of a preterm infant with HH who developed marked feeding intolerance and abdominal distention related to diazoxide treatment which resolved dramatically after discontinuation of the drug. To the best of our knowledge, this is the first reported association between diazoxide and persistent feeding intolerance with abdominal distention in an infant, a condition that should warrant special consideration during follow-up after initiation of treatment.

Case Report

A 19-year-old healthy woman (gravida 1 para 1) was admitted to the hospital due to preterm labor at 31 weeks of gestation. The pregnancy, which had otherwise been unremarkable, was from a non-consanguineous marriage with neither parent having a positive personal or family history for diabetes mellitus. The mother denied use of any medication during gestation. She vaginally delivered a male infant weighing 1720 g (50-75 p, appropriate size for gestational age.), with Apgar scores of 7 and 9 after one minute and five minutes, respectively. Initial physical examination of the infant did not reveal any dysmorphic facial features and organomegaly, and although the patient did not have perinatal asphyxia, he was admitted to due to his prematurity and for having respiratory problems.

During the first 24 hours of follow-up the patient had sustained hypoglycemia, which requires increasing of glucose infusion rate. Persistence of hypoglycemia into the second day of hospitalization prompted evaluation of serum insulin level which was within normal limits (4.8 uIU/ml; range, 2-13 uIU/ml). The hypoglycemia was deemed refractory with subsequent initiation of treatment with hydrocortisone (5 mg/kg/day) while glucose infusion was continued to maintain normoglycemia at a rate of 20 mg/kg/min after placement of a central line. The patient failed to respond to treatment and remained hypoglycemic. Serum insulin level in a blood sample obtained on day 7 of follow-up was found to be elevated (20.7 uIU/ml). Hydrocortisone was discontinued and replaced by diazoxide (Proglycem, Merck Canada Inc., Quebec, Canada) at a dose of 10 mg/kg/day, divided into 3 equal doses every 8 hours. The patient developed severe abdominal distention on the second day and following after diazoxide treatment. Findings on an upright abdominal X-ray were not consistent with intestinal obstruction, while an abdominal ultrasound was unremarkable except for the presence of an increase in intestinal gas. Investigations towards finding the cause of the feeding intolerance and abdominal distention included arterial blood gas analysis and complete blood count as well as evaluation of serum levels of electrolytes, ammonia, renal and liver function tests, thyroid function tests and acute phase reactants were inconclusive. Levels of growth hormone and cortisol were also within

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normal range. Enteral feeding was gradually tapered and discontinued. All intermittently performed hematological and biochemical parameters were within normal limits. Following normalization of blood glucose levels, rate of glucose infusion was reduced gradually with discontinuation of diazoxide on day 28. The abdominal distention was relieved 2 days later, and the patient was recommenced on oral feeding without developing feeding intolerance. He was eventually discharged after 35 days of hospitalization.

Discussion

Hyperinsulinemic hypoglycemia (HH) develops as a result of unregulated secretion of insulin, despite ongoing hypoglycemia [1-4] and should always be considered in the differential diagnosis of patients with refractory hypoglycemia. It usually appears in infants born at term and the occurrence of HH in preterm infants has been thought to be a rare association [4]. It is interesting that macrosomia was not noted in our infant. He did not experienced intrauterine hyperinsulinism or that its occurrence does not lead to macrosomia until the last weeks of pregnancy. The lack of macrosomia is not evidence against the diagnosis.

In a report on 25 children with hyperinsulinism, Dubois et al. highlighted the importance of correctly identifying the underlying cause of hypoglycemia, besides hyperinsulinemia, since it would significantly affect treatment approach. Investigators postulated that a serum insulin level of more than 10 uIU/ml in the presence of hypoglycemia was highly suggestive of hyperinsulinemia, and that it warrants prompt initiation of appropriate treatment [5]. In another report, authors articulated that the ensuing hypoglycemia may be effectively managed by diazoxide without necessitating surgical intervention [6]. We preferred diazoxide for treating of HH following because of an elevated serum insulin level of 20.7 uIU/ml.

Diazoxide is widely accepted to be the first choice of treatment for patients with HH. Under normal circumstances, increased glucose levels result in an increase in intracellular ATP within pancreatic beta-cells. ATPs binds to the inward rectifier potassium channel (Kir 6.2) subunits of ATP-sensitive potassium channels (KATP) resulting in their closure. This is followed by depolarization and subsequently insulin secretion. By binding to regulatory subunits on the sulfonylurea receptor (SUR1), diazoxide keeps the KATP channels open thus preventing insulin secretion [7]. Although the drug is generally well-tolerated, some reports of severe life-threatening adverse effects may be encountered in the literature. Cardiac complications such as heart failure [8,9], hypertrophic cardiomyopathy [10], pulmonary hypertension [8,11], and re-opening of the ductus arteriosus [12] have all been reported in association with diazoxide therapy, with dramatic resolution of symptoms occurring shortly after discontinuation of treatment. In addition, Yildizdas et al. reported on a 4-month-old girl who developed a cardiac complication and neutropenia attributed to diazoxide therapy [8]. Our patient did not develop any cardiac or hematological abnormalities during follow-up. Previous animal studies have demonstrated the presence of presynaptic KATP channels in the gut, which when activated, inhibit Ach release with a consequent decrease in smooth muscle contraction within the gut wall. Diazoxide has been shown to act on these KATP channels, resulting in a decrease in Ach release which translates to reduced colonic motility [13]. Since the peristaltic reflex is dependent on cholinergic transmission, drugs that inhibit the release of Ach would be expected to have an effect on bowel motility [14]. We strongly believe that the feeding intolerance and abdominal distention which developed in our patient were a consequence of a diazoxide-mediated decrease in bowel motility.

Diazoxide proved a useful and effective agent in controlling hypoglycemia in case of HH as in our preterm infant. Treatment was complicated with feeding intolerance and abdominal distention requiring discontinuation of oral feeding; a previously unreported association which we believe warrants consideration during the follow-up of preterm infants being treated with diazoxide. With the more common usage of diazoxide, clinicians should be aware of the adverse effects that may be encountered.

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