

Diazoxide for the Treatment of Hypoglycemia Resulting From Dumping Syndrome in a Child

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Dumping syndrome-associated hypoglycemia is caused by an exaggerated hyperinsulinemic response to glucose absorption in the small intestine. Diazoxide acts on the ATP-sensitive potassium channels and prevents insulin secretion and, thus, should be beneficial for the treatment of hypoglycemia secondary to dumping syndrome. We report on the efficacy of diazoxide in a pediatric patient with dumping syndrome. A 6-year-old girl born at 32 weeks' gestation age with resultant short gut syndrome and liver failure, who had undergone liver, small bowel, and pancreas transplantation at 1 year of age, developed late dumping-like symptoms with postprandial hypoglycemia, headaches, tremors, and irritability. She experienced relief of symptoms with oral intake. An oral glucose tolerance test showed a fasting and 2-hour blood glucose of 3.9 and 2.8 mmol/L, respectively. A gastric emptying study confirmed the diagnosis of dumping. A diet with 2 g of fiber and cornstarch and antimotility medications failed to improve the dumping symptoms. Diazoxide was started orally at a dose of 3 mg/kg/d and was increased to 5 mg/kg/d, divided every 8 hours, after 1 month, with improvement of postprandial blood glucose values (3.6 to 5.0 mmol/L). No hypertrichosis, fluid retention, respiratory concerns, or other side effects were noted. Several duodenal dilations were performed, with resultant improvement of gastric emptying. She was eventually weaned from diazoxide, and no further episodes of substantial hypoglycemia occurred. In conclusion, diazoxide was efficacious and safe for the treatment of hypoglycemia secondary to dumping syndrome in children. It could be of particular use as a bridging therapy for children awaiting more definitive surgical interventions.

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Dumping syndrome-associated hypoglycemia is a constellation of findings caused by an exaggerated hyperinsulinemic response to rapid emptying of a carbohydrate load and glucose absorption in the small intestine. Early symptoms can include bloating, abdominal pain, nausea, vomiting, tachycardia, hypotension, and flushing. These symptoms are triggered by rapid fluid shifts from the plasma into the bowel and the release of vasoactive hormones such as serotonin and vasoactive intestinal polypeptide. Late symptoms (1 to 3 hours postprandial), including dizziness, fatigue, diaphoresis, and weakness, result from postprandial hyperinsulinemic hypoglycemia [1].

Dumping syndrome is a well-known complication of bariatric and peptic ulcer disease surgeries in adults [1, 2] and gastric procedures such Nissen fundoplication in children [3]. Most of the reported data on the pathophysiology, diagnosis, and management of dumping syndrome have resulted from studies or case reports of adults. Calabria *et al.* [4] have demonstrated that children with dumping syndrome will have exaggerated release of glucagon-like peptide-1, leading to insulin hypersecretion and, ultimately, hypoglycemia. This pathophysiologic mechanism has also been reported in adults with dumping syndrome

[5–7]. Treatment of dumping syndrome includes dietary modifications and the addition of cornstarch and acarbose. Octreotide and diazoxide have been used as second-line treatment of dumping syndrome in adults [1, 8, 9]. The use of second-line treatments for dumping syndrome in children has continued to be limited by the scant data for this age group. We report the efficacy of diazoxide in a pediatric patient who had presented with postprandial hyperinsulinemic hypoglycemia in the setting of dumping syndrome.

1. Case Report

A 6-year-old girl had presented to our endocrinology clinic because of concerns of abnormal blood glucose values. Her medical history was notable for prematurity (born at 32 weeks' gestational age), gastroschisis and jejunal atresia, small bowel resection with resultant short gut syndrome, and subsequent liver, small bowel, and pancreas transplantation at 1 year of age because of liver failure. The patient's main nutritional source had been total parental nutrition for most of her life. At ~5 years of age, she was transitioned to gastric feeds through her gastrostomy tube, and celiac disease was also diagnosed. Her stools became "loose" with bolus feeds via the gastrostomy tube, even with a gluten-free diet. Routine laboratory tests revealed hyperglycemia (random blood glucose, 10.6 mmol/L) with hemoglobin A1c of 5.8%, prompting endocrine referral. She had a random blood glucose of 7.2 mmol/L, with an insulin level of 129.7 μ IU/mL (normal range, 3 to 18 μ IU/mL) suggestive of hyperinsulinism. She did not have any signs or symptoms concerning for diabetes mellitus. An oral glucose tolerance test with a 30-mg glucose load (1.75 mg/kg) showed fasting blood glucose and insulin levels of 3.9 mmol/L and 6.5 μ IU/mL and 120-minute blood glucose and insulin levels of 2.8 mmol/L and 5.9 μ IU/mL, respectively. Her ileostomy bag had fully filled twice with loose stools during the first 30 minutes after administration of the glucose load. A gastric emptying study demonstrated that 92% of patient's gastric content had emptied within 1 hour, largely because of a surgical gastroenteric anastomosis created in the past that was bypassing her duodenum. Her duodenum was tortuous with two anastomotic strictures, causing an inability to pass manometry. Both oral contrast and a feeding tube in an upper gastrointestinal study passed preferentially through the gastrojejunostomy rather than the pylorus, likely because of the strictures. Her feeds were changed to 40% carbohydrates, 40% fat, and 20% protein with 2 g of fiber and added cornstarch every 6 hours. Loperamide was started to decrease motility. Despite these interventions, she continued to have episodes of postprandial hypoglycemia, as low as 2.0 mmol/L, with symptoms of headaches, irritability, and tremors, which were relieved by eating. However, she had to eat every 2 hours because her blood glucose levels decreased if she fasted longer. A definitive surgical repair consisting of staged duodenal dilatations was recommended to prevent further dumping. Because of failure of first-line therapy for her dumping syndrome and the persistence of symptomatic hypoglycemia, we discussed adding diazoxide to her treatment plan while patient completed the duodenal dilatations. Her parents gave informed consent to start diazoxide therapy to help with severe hypoglycemia episodes. Diazoxide was started orally at a dose of 3 mg/kg/d, which was increased to 5 mg/kg/d divided every 8 hours after 1 month. Her 2-hour postprandial blood glucose levels had rapidly improved to a range of 3.6 to 5.0 mmol/L, and the episodes of substantial hypoglycemia had resolved (Fig. 1). She continued with diazoxide therapy for a total of 3 months while duodenal dilatations were ongoing. No hypertrichosis, fluid retention, or other adverse effects of diazoxide were noted. The symptoms of dumping had almost resolved at completion of the duodenal dilatations. Diazoxide was slowly weaned, and her blood glucose levels remained in the normal range.

2. Discussion

To the best of our knowledge, the present study is the first reported case of successful treatment with diazoxide for a pediatric patient with postprandial hyperinsulinemic hypoglycemia due to dumping syndrome. Rivkees and Crawford [10] described unsuccessful diazoxide treatment of postprandial hyperinsulinemic hypoglycemia due to dumping

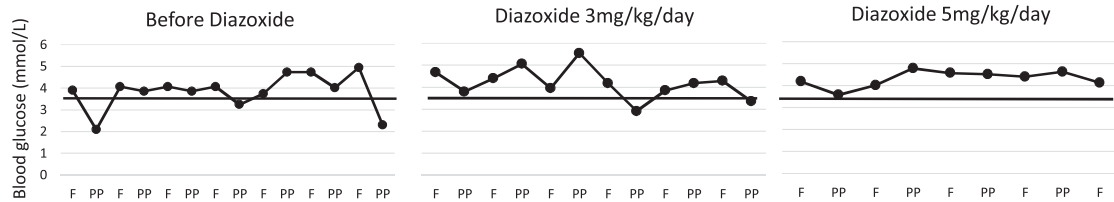


Figure 1. Patient's fasting (F) and 2-h postbreakfast (PP) point of care blood glucose levels before diazoxide, with the lower dose (3 mg/kg/d divided every 8 h) of diazoxide, and with the therapeutic dose (5 mg/kg/d divided every 8 h) of diazoxide. Note the substantial glycemic variation in the blood glucose during the daytime bolus gastric feeds before diazoxide therapy. Before initiation of diazoxide, the patient was eating every 2 h and sometimes even sooner because of the constant concern of hypoglycemia. Severe hypoglycemia resolved with the therapeutic diazoxide dose. Solid black line corresponds to blood glucose level of 3.5 mmol/L.

syndrome in a pediatric patient secondary to Nissen fundoplication (patient 1 in their report). Their patient had experienced more severe dumping, as evidenced by rapid gastric emptying within 20 minutes after a meal and had received diazoxide at a dose of 8 mg/kg/d without adequate glycemic control. In contrast, our patient had achieved euglycemia with a low dose of diazoxide, and this medication proved to be safe, with no side effects noted. The etiology, mechanism, and severity of dumping syndrome were different in our patient compared with the patient's case reported Rivkees and Crawford [10]. In our patient, a substantial portion of her gastric content was dumped directly into the jejunum from her stomach through her anastomosis. Also, although most of her gastric content had emptied within 20 minutes after a meal, she had some residual content that had emptied within the first hour. Because the diazoxide therapeutic dose in children is 5 to 15 mg/kg/d, one could suggest that therapeutic failure should not be diagnosed until an inadequate glycemic response has occurred with the maximum dose of diazoxide, barring any side effects that would prevent dose increases.

Diazoxide is a benzothiadiazine that has both antihypertensive and hyperglycemic properties. Its hyperglycemic activity results from interacting with ATP-sensitive potassium channels in the membrane of pancreatic β cells. By allowing sustained potassium efflux from the β cell, it prevents depolarization of the cell membrane, thereby blocking further steps in the insulin release pathway. Diazoxide has been widely used in children for the treatment of congenital hyperinsulinemic hypoglycemia. However, its use for pediatric dumping syndrome has been anecdotal. Case reports of adults with dumping syndrome have described the clinical utility of using diazoxide for cases in which dietary modifications and acarbose have failed to improve symptoms and blood glucose levels [1]. The use of diazoxide in pediatric patients requires close follow-up to monitor for serious side effects. However, in our patient, diazoxide proved to be safe at a low therapeutic dose. Longer term studies are needed to facilitate knowledge on the efficacy and patient safety with the prolonged use of diazoxide for dumping syndrome in children. Newer alternative therapies such as exendin-(9-39), a glucagon-like peptide-1 receptor antagonist, are promising and are being studied for this indication [4].

Diazoxide could be an efficacious and safe therapeutic option for the treatment of hypoglycemia secondary to dumping syndrome in children. It might be especially useful as bridging therapy for children awaiting more definitive surgical interventions after first-line therapies have failed to provide glycemic improvement. Longer term clinical trials, however, are needed to determine its efficacy and safety.

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