Diazoxide treatment for persistent hypoglycemia in a small for gestational age preterm infant with adequate low insulin levels

Abstract: Small for gestational age (SGA) newborn infants can have prolonged hypoglycemia due to diminished glycogen stores, diminished alternative energy substrates, or hyperinsulinism. Recurrent episodes of hypoglycemia are strongly correlated with persistent neuro-developmental and physical growth deficits. Treatment includes glucose supplements or medications affecting insulin secretion, gluconeogenesis, or glycogenolysis. Diazoxide suppresses insulin secretion by acting as an ATP-sensitive potassium channel agonist to prevent membrane depolarization, calcium influx, and insulin secretion. Therefore, it is used in persistent hypoglycemia of neonates associated with hyperinsulinism. We report a case of a female SGA preterm infant who had persistent hypoglycemia (>2 weeks of age) with low adequate serum insulin levels and no other clear biochemical evidence of hyperinsulinism or other abnormalities. As a result of an inability to control her glucose levels without high intravenous levels of glucose and continuous glucagon infusion, she was treated successfully with diazoxide, which was discontinued when the infant reached 5 kg. No side effects were noted. In rare cases of persistent hypoglycemia, and a need for very high glucose infusion rate with adequate low insulin levels even without biochemical evidence supportive of hyperinsulinism, diazoxide treatment can be offered with close monitoring of glucose levels and possible side effects. The exact mechanism is not clear and deserves further evaluation.

Keywords: Diazoxide; hypoglycemia; insulin; preterm; small for gestational age.

Introduction

Neonatal hypoglycemia is common among small for gestational age (SGA) preterm infants after birth, primarily due to diminished glycogen stores and diminished alternative energy substrates. Some SGA preterm infants will experience transient or persistent hypoglycemia with hyperinsulinism. The mechanism of transient hyperinsulinemic hypoglycemia is unclear, as opposed to persistent hyperinsulinemic hypoglycemia of infancy that is associated with genetic defects in ATP-sensitive potassium (KATP) channels (composed mainly of Kir6.2-type subunits and sulfonylurea receptor subunits) of the pancreatic beta cells, causing inadequate autonomous insulin secretion unrelated to glucose serum levels [1].

Diazoxide is used to treat hypoglycemia that is associated with hyperinsulinism. It suppresses insulin secretion by acting as a KATP channel agonist to prevent membrane depolarization, calcium influx, and insulin release [1]. We describe a female SGA preterm infant with persistent hypoglycemia (>2 weeks of age) with low adequate serum insulin levels and no other evidence of hyperinsulinism, except for a need for very high glucose infusion rate. As a result of an inability to stop intravenous glucose and glucagon therapy, she was treated successfully with diazoxide.

Presentation of the case

A preterm, female infant was born at 28 weeks of gestation to a 28-year-old G1P0 mother after pregnancy was induced by clomiphene citrate. During pregnancy, serial ultrasounds revealed fetal growth retardation with oligohydramnios. In utero studies included normal karyotype, 46XX, and amniocentesis was negative for cytomegalovirus and toxoplasmosis. Fetal echocardiography was normal. A cesarian section delivery was performed due to non-reassuring fetal monitoring. Birth weight was 620 g (7th percentile) and head circumference 22.8 cm (4th percentile). From birth, hypoglycemia requiring continuous...
glucose supplementation, up to 20 mg/kg/min and continuous glucagon infusion therapy up to 1 mg/day, were needed in order to maintain serum glucose levels within normal values. Laboratory evaluation, including complete blood count, chemistry, acid-base balance, thyroid function, ACTH test, blood ammonia, free fatty acid levels, galactose 1 phosphate uridyl transferase levels, and metabolic screen (amino acids, very long chain fatty acids, acylcarnitines and lactate/pyruvate in blood and organic acids in urine) were within normal limits. A glucagon test resulted in a normal rise of glucose. Growth hormone and cortisol levels taken during hypoglycemia, (glucose <40 mg %) were adequately high. Insulin levels, taken twice, were adequately low, 0.7 mU/L and <0.1 mU/L (n<5 mU/L), respectively. Levels of β-hydroxybutyrate during hypoglycemia were 2 mmol/L, higher than expected in hyperinsulinism. Sequencing did not reveal mutations in ABCC8/KCNJ11, genes associated with persistent hyperinsulinemic hypoglycemia of infancy.

As a result of an inability at the age of 3 months to stop glucose infusion and a need for continuous IV glucagon therapy despite continuous feeding enriched with glucose polymers, and because of the desire to switch to a medication allowing for discharge of the infant, we did not consider other intravenous drugs, such as somatostatin. After obtaining institutional and parental approval, we started treatment with oral diazoxide, at the dosage of 2 mg/kg/day together with hydrochlorothiazide (2 mg/kg/day) to control for possible fluid retention. The infant’s weight at that point was 1872 g. Within 48 h, glucose levels increased to 760 mg %, which gradually decreased to normal levels after adjusting the diazoxide dose to 0.5 mg/kg/dose, BID (twice daily). Weaning from IV glucose and glucose polymers was successfully achieved within 2 weeks. Echocardiography completed during treatment with diazoxide showed no signs of pulmonary hypertension and closed ductus arteriosus. No arterial desaturation (<90%) or bradycardias (<100 beats per minute) were documented during treatment. The infant was discharged home on interval breast milk feeding. Diazoxide was stopped successfully when the infant reached 5 kg.

Discussion

We have described a symmetric SGA preterm infant with persistent hypoglycemia and low adequate levels of insulin with no other clear biochemical evidence of hyperinsulinism. Due to the failure of maintaining glucose levels in the normal range without intravenous glucose supplement and glucagon treatment for 3 months, she was treated successfully with diazoxide. A recent study characterizing the phenotype and genotype of neonates born SGA that developed hyperinsulinemic hypoglycemia, showed that plasma insulin levels can be undetectable during hypoglycemia in this group. However, other biochemical signs of hyperinsulinism, such as β-hydroxybutyrate and non-esterified fatty acids, were low during hypoglycemia in all study infants [1].

In our infant, the need for a very high glucose infusion rate suggested the diagnosis of hyperinsulinemic hypoglycemia. In contrast, the low or even undetectable insulin levels during hypoglycemia, and the high β-hydroxybutyrate levels, did not support this diagnosis. A possible explanation for the high intravenous glucose infusion rate required to maintain normoglycemia with the low insulin levels, and the increased beta-hydroxybutyrate and normal serum levels of fatty acids, could be related to the finding that some SGA infants display low insulin levels with increased insulin sensitivity with respect to glucose disposal, but not with respect to suppression of lipolysis [2]. The preterm infant was treated with very high dose glucagon (1 mg per day). This high dose of glucagon can paradoxically lead to insulin secretion and might explain our inability to stop glucagon and glucose treatment. Furthermore, in differentiating hyperinsulinemia from non-hyperinsulinemic causes of neonatal hypoglycemia, infants with hyperinsulinism had significantly lower plasma glucose concentrations, higher serum insulin/glucose levels (usually >0.4), absent ketones and exaggerated plasma glucose response to glucagon administration, usually >30 mg/dL above the baseline value. Our patient had none of the above parameters, making the possibility of hypoglycemia due to hyperinsulinism levels less likely. Therefore, it seemed that diazoxide would not be helpful and it was not immediately offered as a treatment.

Another possible explanation for persistent hypoglycemia with low insulin levels could be cortisol or growth hormone deficiency, which is associated with increased insulin sensitivity, decreased insulin secretion and decreased fasting glucose concentrations. However, growth hormone level during hypoglycemia was adequately elevated and cortisol response to ACTH test was normal.

Diazoxide suppresses insulin secretion by acting as a KATP channel agonist to prevent membrane depolarization, calcium influx, and insulin release. Therefore, it has been used in neonates with hypoglycemia and hyperinsulinism [1]. Diazoxide has potential benefits for preterm infants besides preventing persistent hypoglycemia. It
has been shown to promote oligodendrocyte, precursor cell proliferation and myelination, and to prevent hypoxia-induced periventricular white matter disease in rats [5]. However, high sodium levels and fluid retention are commonly associated with diazoxide treatment. Diazoxide can induce pulmonary arterial hypertension with re-opening of the ductus arteriosus, hypoxia, and cardiac arrest [4]. Hypertrophic cardiomyopathy after prolonged treatment with diazoxide has been reported [5]. Furthermore, severe feeding intolerance and abdominal distention was described in a preterm infant following diazoxide treatment [3]. Therefore, diazoxide should be given to neonates with extreme caution. We witnessed hyperglycemia (760 mg/dL) when starting at a diazoxide dose of 2 mg/kg/dose, which was normalized after reducing diazoxide dose to 0.5 mg/kg/dose, BID. Of note is that hyperglycemia has been found to be associated with severe intraventricular hemorrhage in preterm infants, but repeated cranial ultrasounds were normal in our patient.

In summary, we describe a SGA preterm infant who had persistent hypoglycemia with adequate low insulin levels and no other clear biochemical evidence of hyperinsulinism. A high glucose intake (up to 20 mg/kg/min) and a continuous glucagon infusion to maintain normal blood glucose levels was required, however, the infant eventually responded quickly to diazoxide therapy. Moreover, the dramatic glucose response (760 mg/dL) to a very low dose of diazoxide (2 mg/kg/dose, BID) should be noted, suggesting that a lower dose be administered in such cases. The need for a very high glucose infusion rate and the remarkable sensitivity to diazoxide therapy suggests that this patient had hyperinsulinemic hypoglycemia with low insulin levels. The exact pathogenesis of the persistent hypoglycemia and the mechanistic response to diazoxide is not clear. This treatment could be offered in very low doses for the management of persistent hypoglycemia in SGA infants who are not responsive to other treatment modalities. However, as detrimental side effects were reported with diazoxide and drug safety could not be determined from a single case description, diazoxide should be administered with caution until safety may be ascertained from additional case reports.

Received February 25, 2013. Accepted November 4, 2013. Previously published online November 22, 2013.

References


The authors stated that there are no conflicts of interest regarding the publication of this article.