Diazoxide-Induced Hypertrichosis in a Neonate With Transient Hyperinsulinism

Clinical Medicine Insights: Case Reports
Volume 16: 1–4

DOI: 10.1177/11795476231151330

Seyyed Javad Boskabadi[1], Sima Ramezaninejad[1], Masoumeh Sohrab[1] and Roya Farhadi[2]

[1]Department of Clinical Pharmacy, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran. [2]Department of Neonatology, Pediatrics Infectious Diseases Research Center, Mazandaran University of Medical Sciences, Sari, Iran.

ABSTRACT: Diazoxide is one of the FDA-approved pharmacologic treatments for hyperinsulinemic hypoglycemia, however, its adverse effects in infants are not well described. We reported a 37-week-old boy with the diagnosis of hypoglycemia. We started a dextrose infusion, but we used oral diazoxide, due to hypoglycemia episodes despite the increase in dextrose intake. The newborn had a normoglycemic condition after gradually increasing the diazoxide dose to 15 mg/kg/day. He was fully breastfed and discharged at 14 days of age with ongoing diazoxide. In weekly serial clinical follow-ups, the parents noticed an increase in the growth of forehead and facial hair that was diagnosed as diazoxide-induced hypertrichosis. Diazoxide was gradually tapered, and hypertrichosis continued until 1 month after dioxide discontinuation. Diazoxide use in NICU settings has increased over time. Diazoxide has many side effects, one of which is hypertrichosis. Many diazoxide side effects have been reported in adults or children and few studies have reported the prevalence of these adverse effects of diazoxide in neonates and infants.

KEYWORDS: Hyperinsulinemia, diazoxide, hypertrichosis, drug safety, side effect

RECEIVED: November 25, 2022. **ACCEPTED:** December 28, 2022.

TYPE: Case Report

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: Roya Farhadi, Department of Neonatology, Pediatrics Infectious Diseases Research Center, Mazandaran University of Medical Sciences, Sari, Iran; Division of neonatology, Department of Pediatrics, Boo Ali Sina Hospital, Pasdaran Boulevard, P.O.Box 48158-38477, Sari, Iran. Emails: rfarhadi@mazums.ac.ir; dr.royafarhadi@gmail.com

Introduction

Congenital hyperinsulinism is a rare disease characterized by excessive insulin secretion by the pancreatic beta-cells leading to hypoglycemia.[1] This disease manifests with transient or persistent neonatal hypoglycemia. Blood glucose level alterations usually occur in the first hours after birth and may last for some days. Low blood glucose level is natural in the first hours since glucose sources are changed from a mother as a continuous source to breastfeeding as an intermittent source.[2]

Transient hyperinsulinism (HI) is the most common cause of severe infantile hypoglycemia.[3] The etiology of HI is unknown. Birth asphyxia, prematurity, gestational diabetes, maternal diabetes, low birth weight, or macrosomia may lead to transient HI.[4] In this situation, it is assumed that intermittent maternal hyperglycemia leads to fetal hyperglycemia leading to hypertrophy and elevated function of pancreatic beta cells leading to embryonic and neonatal hyperinsulinemia.[5,6]

Up to 15% of term infants experience more severe or persistent hypoglycemia that can be associated with long-term brain damage and neurodevelopmental delays.[7]

The essential treatment of transient hyperinsulinemia includes intravenous dextrose, diazoxide, and proper nutrition.[8] The next important step is to determine whether the infant responds to diazoxide or not. Diazoxide is the first line and the only FDA-approved oral medication approved for the treatment of HI. It is a sulfonylurea receptor agonist, which opens ATP-sensitive potassium channels at β cells and inhibits insulin secretion.[9]

Various side effects have been reported for diazoxide, but the prevalence of its use and adverse effects in the neonatal period are not well defined.[7,10]

In the present case report, hypertrichosis due to diazoxide is reported in an infant with hyperinsulinism.

Case Presentation

This study complies with the Declaration of Helsinki's ethical standards. The 37-week-old boy was born with a birth weight of 3800 g (G2P2Ab0) following cesarean section due to fetal distress. Apgar scores at birth were 9 and 10, and the infant had mild grunting at birth.

His mother developed gestational diabetes at 22 weeks of gestation, which was under control by insulin injection and the parents of the infant were not relatives and were healthy; moreover, the first child of the family did not have a history of any problems.

In the first examination of the neonate at the second hour of life, plasma glucose was 25 mg/dl. The infant was transferred to the neonatal intensive care unit (NICU) with the diagnosis of hypoglycemia. We started a dextrose infusion (2 CC/kg of serum D10%W) as a bolus and 6 to 8 mg/kg/minutes of a continuous infusion of 10% dextrose and water (D10%W).

The patient's plasma glucose reached 35 mg/dl 2 hours later; then, the serum infusion of D10W% was increased to 12 mg/kg/minutes and then to 15 mg/kg/minutes through the umbilical central vein catheter. Due to the non-availability of glucagon in our center, it was not possible to administer this drug to the

baby, so we increased the infusion of D10W%. Despite the general improvement in the baby's condition and the onset of breastfeeding, we had to increase the rate of dextrose infusion to 20 mg/kg/minutes on the third day of birth due to hypoglycemia episodes. Oral diazoxide (oral capsule 100 mg, Proglicem, product of Merck Sharp & Dohme Company, USA) was started with the initial dose of 10 mg/kg/day divided into 3 times a day. The newborn had a normoglycemic condition after gradually increasing the dose to 15 mg/kg/day.

With suspicion of hyperinsulinemia, the blood insulin level was checked before starting diazoxide. The insulin level of 89 µU/ml (normal range 8-13 µU/ml) was reported with simultaneous glucose of 24 mg/dl.

Complete abdominal ultrasonography was normal, and cardiac echocardiography reported left ventricular hypertrophy without heart failure symptoms.

Endocrinology counseling was performed for the neonate. Further evaluations showed normal cortisol levels, growth hormone, and blood lactate. Urinary ketones, reducing substances, and amino acids were negative. Gradually, the baby was fully breastfed, the IV line was discontinued, and the neonate was discharged at 14 days of age with ongoing diazoxide therapy. Considering that the infant had a diabetic mother the final diagnosis was transient hyperinsulinism.

In weekly serial clinical follow-ups, blood glucose was 50 to 70 mg/dl at the age of 28 days when the parents noticed an increased growth of facial hair on the baby's forehead. This was later diagnosed as diazoxide-induced hypertrichosis (Figure 1).

Diazoxide was gradually tapered, and on day 40, the infant's plasma glucose level was 70 mg/dl; the dose tapering was done with caution, and at the age of 58 days, diazoxide was discontinued. Glucose and insulin levels were normal 1 week later.

Hypertrichosis continued until 1 month after dioxide discontinuation. Then the infant's family migrated to another city, so we were only able to follow up by phone. The family announced the complete elimination of excess hair growth at the age of 4 months. The infant was in good condition in terms of neurodevelopmental growth.

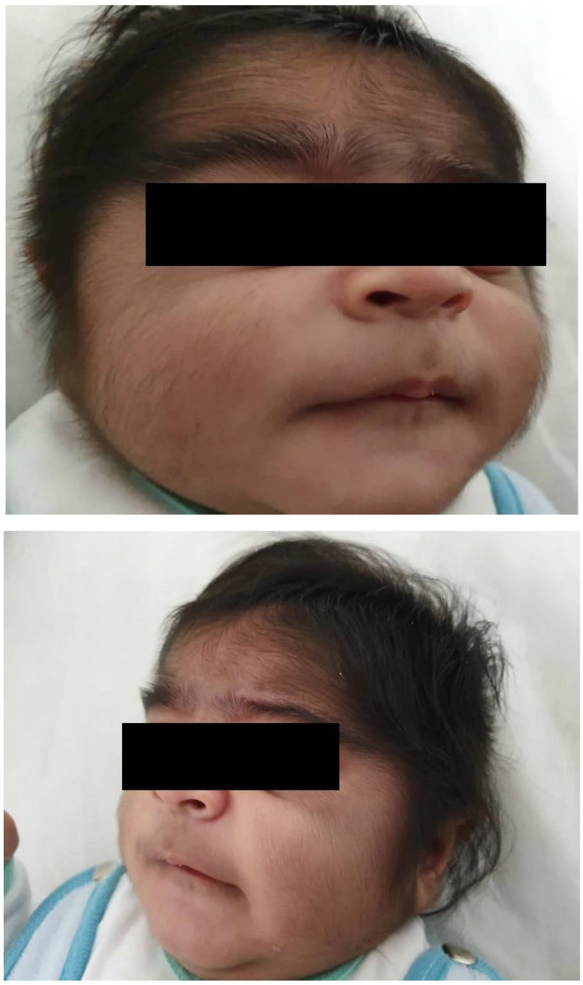

Figure 1. Diazoxide-induced hypertrichosis (1 month after treatment).

Discussion

Neonatal transient hyperinsulinemia is an important diagnosis associated with long-term hospitalization, nutritional problems, and serious long-term consequences due to hypoglycemia. Rapid identification of transient or persistent forms and genetic testing are important to reduce the recovery period and optimize treatment modality. On the other hand, early diagnosis and management of HI, are essential for the prevention of neurological damage occurring as a direct consequence of prolonged hypoglycemia.[11]

Neurological damage is present in one-third to half of the children with early onset HI. Importantly, neurodevelopmental damage is observed in both transient and permanent forms of HI and in both mild and severe forms of HI emphasizing the need to recognize and manage hypoglycemia as early as possible.[12]

Diazoxide is the first line of treatment for HI and the only FDA-approved drug for hyperinsulinism. Historically, diazoxide was used for the treatment of severe hypertension and hyperglycemia is one of its side effects.[13] Its action on the pancreatic b-cells opens the K+ ATP channels

(ATP-sensitive potassium channels), thereby inhibiting insulin. It is given at the dose of 5 to 20 mg/kg/day, PO, divided into 3 doses. *Hyperglycemic effect* with *oral administration occurs within 1 hour*, with a *half-life* of *8 hour*.[14]

Diazoxide-related serious adverse events include necrotizing enterocolitis,[15,16] pulmonary hypertension,[17,18] sodium and fluid retention,[19,20] edema,[20,21] neutropenia,[22,23] anemia,[24] thrombocytopenia,[25,26] and hyperuricemia.[27] In addition, rapid administration of diazoxide (intravenous) may cause severe hypotension.[28,29] Refractory hypotension and cerebral insufficiency after diazoxide administration was also reported.[30]

In 2015, the FDA announced a black box warning, that diazoxide may lead to pulmonary hypertension in infants.[13] The most common side effect is mild-to-severe hypertrichosis, which is thought to depend on the dose for each patient.[23]

Table 1. Clinical characteristics of infants with hyperinsulinemic hypoglycemia that received diazoxide and had Hypertrichosis.

REFERENCES	TYPE OF STUDY	PATIENT(S) AGE[a]	MEAN DOSE OF DIAZOXIDE (MG/KG/D)	OUTCOME
Chandran et al[33]	Observational	36.4 ± 2 wk	3-5	Hypertrichosis occurred in 2 infants[b]
Fukutomi et al[34]	Retrospective	<1 y	6.9 ± 3.1	Hypertrichosis occurred in 8.6%
Loke et al[35]	Case report	6 mo	12.6	Diazoxide was replaced with sirolimus for hyperinsulinemic hypoglycemia treatment

[a]The age that hypertrichosis occurred.
[b]Total patients was 56 infants.

Hypertrichosis is reported at a rate of 45% (in adults) but is well tolerated.[10] The underlying pathophysiology resulting in hypertrichosis is related to the effect of diazoxide on 2 potassium-gated channels in the skin that affect hair growth, namely, SUR1/KIR6.2 and SUR2B/KIR6.1, resulting in lengthening of the anagen phase of hair growth.[31,32]

Although diazoxide has serious side effects, controlling hyperinsulinemia in the baby is much more critical. So, diazoxide use in NICU settings has increased over time. On the other hand, many side effects have been reported for diazoxide in adults or children and few studies have reported the prevalence of its adverse effects in neonates and infants. In addition, little data exist regarding the number of neonates who continue diazoxide following discharge from the neonatal ward.[7]

Our patient received 15 mg/kg/day of diazoxide and after 1 month, he suffered hypertrichosis. Table 1 demonstrated some clinical reports and factors associated with diazoxide-induced hypertrichosis. As shown in Table 1, based on a few data, the cumulative dose was an important risk factor for Hypertrichosis.

Hypertrichosis (in particular on the back and limbs) is dose-dependent and is usually reversible with dose reduction or discontinuation. Doses greater than 15 mg/kg can cause more adverse effects, so the recommended approach is beginning at low doses and titrating diazoxide based on plasma glucose levels.[27,36] If hypertrichosis does not respond to reducing the dose of diazoxide, stopping diazoxide and using alternative treatment options such as octreotide or sirolimus are recommended for the treatment of hyperinsulinism.[36]

Hypertrichosis is a known side effect of diazoxide and there are few neonatal or infant reports in the literature discussing the side effects of this agent, specifically hypertrichosis.

Due to the fear of serious side effects caused by diazoxide, this drug is started with lower doses and gradually increased in infants. In this case, diazoxide was started with a higher dose than the previous cases, no life-threatening side effects were seen, and on the other hand, hypertrichosis was resolved over time by reducing the dose and stopping the drug. To the best of our knowledge this is the first case of newborn using such high dose without any other side effects except hypertrichosis.

Eventually, reports of cases or prospective cohort studies are necessary to provide more detailed information on adverse effects associated with its use in neonates.

Conclusion

Diazoxide is the only FDA-approved drug for HI treatment. One can also use glucagon and a glucose infusion as a temporary measure until the effects of diazoxide stabilize glucose levels. In addition, diazoxide should be started with the appropriate dose and monitored to prevent dangerous complications.

Author Contributions

R.F, S.J. B, S.R, and M.S involved in the interpretation, collecting of data, and writing the original draft of the manuscript. S.J.B and R.F were involved in editing the final version of the manuscript. All authors reviewed the paper and approved the final version of the manuscript.

Availability of Data

The data are available from the corresponding author upon reasonable request.

Ethical Approval

The study was approved by our local ethics committee.

Informed Consent

Written informed consent was obtained from the infant's legal guardian, for the publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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