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ORIGINAL ARTICLE

Development of Pulmonary Hypertension During Treatment with Diazoxide: A Case Series and Literature Review

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Abstract Congenital hyperinsulinism (CHI) is the most common cause of persistent hypoglycemia in infancy. The mainstay of medical management for CHI is diazoxide. Diazoxide inhibits insulin release from the pancreas, but also causes smooth muscle relaxation and fluid retention so it is typically given with chlorothiazide. In July 2015, the FDA issued a drug safety communication warning that pulmonary hypertension (PH) had been reported in 11 infants being treated with diazoxide and that the PH resolved with withdrawal of diazoxide. All three of the cases in our hospital were admitted to the neonatal intensive care unit (NICU) for hypoglycemia. All patients received thorough radiologic and laboratory evaluations related to their diagnosis of CHI. All initially improved when diazoxide was initiated. Case 1 and case 3 were discharged from the NICU on diazoxide and chlorothiazide. Case 2 developed pulmonary hypertension while still in the NICU days after an increase in diazoxide dosing. Case 1 presented to the emergency room in respiratory distress shortly after discharge from the NICU with evidence of PH and heart failure. Case 3 presented to the emergency room after 2 weeks at home due to a home blood glucose reading that was low and developed PH and heart failure while an inpatient. Discontinuation of diazoxide led to resolution of all three patients' PH within approximately one week. The experience of our hospital indicates that pulmonary hypertension may be more common than previously thought in infants taking diazoxide. It is unclear if these symptoms develop slowly over time or if there is some other, as yet undescribed, trigger for the pulmonary hypertension. Our hospital's experience adds to the body of evidence and suggests these infants may benefit from more surveillance with echocardiography.

Keywords Congenital hyperinsulinism · Pulmonary hypertension · Diazoxide · Circulatory overload

Introduction

Congenital hyperinsulinism (CHI) is the most common cause of persistent hypoglycemia in infancy [1]. The definition of CHI is unsettled in the literature [2–7], though it is generally described as requiring four elements: (1) an inappropriately elevated insulin level during hypoglycemia; (2) a requirement of a supraphysiologic glucose infusion rate; (3) an appropriate glycemic response to glucagon; (4) suppression of free fatty acid and ketone production during hypoglycemia.

The mainstay of medical management for CHI is diazoxide, a benzothiadiazine, historically studied as an antihypertensive and incidentally noted to cause hyperglycemia in patients [8, 9]. Diazoxide is available in tablet form (Proglycem, FDA approved in 1976) to treat symptomatic hypoglycemia [10]. It is also available intravenously and indicated as a peripheral vasodilator for emergency reduction of severe hypertension [16]. Diazoxide acts to open K_{ATP} channels throughout the body; in the pancreatic beta-cells this serves to inhibit insulin release from the cells and in smooth muscle cells this leads to local relaxation. Common side effects of diazoxide are

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hypertrichosis, fluid retention, and electrolyte disturbances; less common side effects are ileus, coarsening of facies, neutropenia, hyperosmolar coma, gout, and heart failure. In July of 2015, the FDA issued a drug safety communication warning that pulmonary hypertension (PH) had been reported in infants being treated with diazoxide which resolved with withdrawal of diazoxide [11]. Here, we report a case series of three infants at our medical center who developed pulmonary hypertension while taking diazoxide for transient CHI. All patients had resolution of their PH after withdrawal of diazoxide.

Case Series

Case 1

A male infant was born at 35 weeks gestation via cesarean section for preeclampsia and oligohydramnios. Prenatal labs were unremarkable, and delivery was uncomplicated. At birth he was noted to be small for gestational age. He was admitted to the neonatal intensive care unit (NICU) within hours of birth for severe hypoglycemia. During his NICU stay, he continued to have detectible insulin levels during episodes of hypoglycemia. He did not routinely require supra-physiologic glucose infusion rates (peak GIR was 5.4 mg/kg/min in addition to enteral feeds) but was unable to be weaned from continuous intravenous dextrose, even with nutritional fortification and frequent feedings.

He was carefully evaluated for possible causes for persistent hypoglycemia that led to a diagnosis of perinatal-stress induced hyperinsulinism. The patient was initiated on diazoxide every 12 h (with parallel dosing of chlorothiazide) on day of life 13. Thereafter, he had rapid improvement in his blood glucose levels allowing for a rapid decrease of his glucose infusion rate. Prior to discharge from the NICU, he required an increase in his diazoxide dose interval to every 8 h to enable him to fast at least 8 h. At 12 weeks of life, he presented with significant respiratory distress, poor distal perfusion, a gallop rhythm, and cardiomegaly on chest x-ray. An echocardiogram showed a dilated right ventricle with elevated pulmonary pressures at 3/4 of systemic pressures.

He was immediately admitted to the pediatric intensive care unit where his diazoxide and chlorothiazide were discontinued based on the institution's prior experience. In the PICU, the patient received oxygen and noninvasive positive pressure ventilation for his PH, and he was evaluated for other possible causes for his acute presentation. Over the ensuing days, following discontinuation of diazoxide, the patient improved with normalization of his echocardiogram and no further therapies. He was discharged home on hospital day 12.

Case 2

A male infant was born at 40 weeks gestation via spontaneous vaginal delivery. Prenatal labs were unremarkable. Delivery was complicated by terminal meconium and prolonged rupture of membranes. At approximately 1 h of life, the infant was transferred to the NICU for tachypnea. On initial lab evaluation, the infant was found to be hypoglycemic (glucose 26 mg/dL). His initial physical exam was concerning for Beckwith-Wiedemann Syndrome (BWS) due to the constellation of macrosomia (86th percentile for birth weight), neonatal hypoglycemia, macroglossia, and posterior ear creases.

Over the next 2 days, persistent hypoglycemia drove increases in the patient's glucose infusion rate (GIR) to a peak of 15 mg/kg/min on hospital day 3. A critical lab evaluation during hypoglycemia (serum glucose 50 mg/dL) demonstrated an insulin measurement of 12.2 mcIU/mL with suppressed free fatty acids and low ketones; findings consistent with hyperinsulinemic hypoglycemia. Due to the increased fluid volume with a supra-physiologic GIR, diazoxide was initiated at 8 mg/kg/day divided three times daily. After 1 day the diazoxide dose was increased to 12 mg/kg/day. On the third day of diazoxide therapy, the patient developed tachypnea and was initially treated with two doses of IV furosemide due to fluid retention and then started on scheduled chlorothiazide.

He continued to develop worsening tachypnea and progressed to hypoxic respiratory failure requiring escalating ventilator settings. An echocardiogram on hospital day 5 revealed supra-systemic pulmonary artery pressures. He was started on inhaled nitric oxide (iNO) for PH but continued to require escalating ventilator support and iNO dosing (up to 20 ppm) for management. His diazoxide was decreased to 8 mg/kg/day on hospital day 9 and another echocardiogram was performed on hospital day 11 showing improvement, but not resolution, of his PH. At that time, diazoxide was discontinued and a 5-day course of dexamethasone was initiated, primarily to manage the patient's respiratory symptoms. The patient's glucose levels remained >50 mg/dL without need for elevated glucose infusion rates, frequent feedings, or insulin secretagogues even after the dexamethasone was discontinued. He was discharged home on hospital day 40. He was followed with serial echocardiograms which showed normalization of his pulmonary pressures over the subsequent month.

Case 3

A male infant was born at 36 weeks via induced vaginal delivery. Maternal history was significant for pre-eclampsia and A2 gestational diabetes. There were no clinical concerns until 30 h of life when he was noted to have a

hypoglycemic seizure. During the ensuing NICU admission, he was diagnosed with hyperinsulinism which was diazoxide-responsive. He underwent an echocardiogram on day of life 4 (due to the association of maternal diabetes and congenital heart disease) that was unremarkable prior to initiation of diazoxide therapy. His NICU course was additionally complicated by a partial exchange transfusion for polycythemia. The patient was discharged home on diazoxide (13 mg/kg/day divided three times daily) and hydrochlorothiazide (2 mg/kg/day divided two times daily) on day of life 14.

He was subsequently admitted to the hospital on day of life 29 due to several episodes of hypoglycemia that had been treated at home with intramuscular glucagon. On hospital day 3, he was noted to have an abnormal pulmonary exam, hepatomegaly, and a chest X-ray showing cardiomegaly, increased pulmonary vascular markings, small pleural effusions and pulmonary edema. An echocardiogram showed dilation of all cardiac chambers, decreased biventricular systolic function, and pulmonary artery pressures approximately 2/3 of systemic pressures. The diazoxide was discontinued due to the echocardiographic findings. The patient was treated with diuretics to address the pulmonary findings and hepatomegaly and he was empirically started on physiologic hydrocortisone.

On hospital day 6, a repeat echocardiogram showed resolution of bilateral systolic dysfunction, moderate tricuspid regurgitation, trace mitral regurgitation, interval improvement in ventricular size, and normal pulmonary artery pressures.

The patient was unable to maintain adequate blood glucose levels when tested with a fast, with glucose levels down to 24 mg/dL 6 h post feed. A critical lab sample during this episode of hypoglycemia remained consistent with hyperinsulinism (insulin 2.3 mIU/mL, free fatty acids 0.56 mmol/L, growth hormone 11.4 ng/mL). He was treated with glucagon, which resulted in euglycemia, and hydrocortisone was continued to treat his hyperinsulinemia.

On hospital day 11, echocardiography showed continued diastolic dysfunction, normal biventricular systolic function, and resolution of the tricuspid and mitral regurgitation. Additionally, pro-brain natriuretic peptides (pro BNP) were evaluated on hospital day 10 (1849 pg/mL), 14 (673 pg/mL), 17 (759 pg/mL), 32 (405 pg/mL).

The patient was ultimately discharged from the hospital on hydrocortisone therapy and frequent feedings with home blood glucose checks.

Discussion

In the literature, two distinct categories exist describing severe diazoxide-related adverse effects: cardiac effects resulting from fluid retention and volume overload with subsequent congestive heart failure (CHF) [12] and distinct pulmonary hypertensive adverse effects [13–15]. The former effect is much more frequently seen when diazoxide is given without concurrent administration of a thiazide diuretic to counteract the salt and water retention that are known side effects of diazoxide therapy alone. In some cases, both volume overload and pulmonary hypertension were witnessed [16, 17].

Review of the published cases, as well as those reported here, reveals little consistency in the time-to-effect. The most consistent observation is that the circulatory side effects did not seem to be present at doses below 10 mg/kg/day, though in the second case described here, the pulmonary hypertension persisted when the dose was decreased from 12 mg/kg/day to 8 mg/kg/day, and only resolved once the diazoxide was discontinued entirely. It is not clear if the PH would have completely resolved at the lower dose with more time.

The FDA's recent drug safety communication indicates that there have been 11 case reports of circulatory adverse events since the drug's approval in 1973. The experience of our hospital implies that the occurrence of this idiosyncratic adverse effect may be higher than previously thought. No patients, to our knowledge, have had echocardiograms while on diazoxide prior to the development of the described side effects. Therefore, it is unclear if these symptoms develop slowly over time or if there is some other, as yet undescribed trigger for the pulmonary hypertension.

The mechanism has been posited [19] to be direct cardiac toxicity. Available literature on human tissues is silent on possible mechanisms. Studies looking at the effect of K_{ATP} channel activation on human pulmonary tissue tend to show a vasodilatory effect [18]. Investigations of the mechanism by which diazoxide imparts cardiac protection from ischemia [19] have noted the promiscuity of diazoxide effecting multiple receptors and the paucity of understanding of its effects on other ion channels, ATPases, and mitochondrial energetics. The dose dependence that seems to crop up in prior case reports, as well as in our case series, may implicate a dose-dependent interaction of diazoxide with these other proteins once the K_{ATP} interaction has been saturated. In the 1970s and 1980s, when diazoxide was a newer medication, the literature contains reports of it being used experimentally as an agent to *treat* pulmonary hypertension. One of the first case reports of diazoxide as treatment of PH [20] demonstrated a decrease in pulmonary and systemic vascular resistance attributable to diazoxide; however, there are also case series evaluating this intervention [21] with catastrophic results.

In conclusion, infants who appear ill while receiving diazoxide require prompt evaluation for pulmonary hypertension. As awareness of this unpredictable reaction

continues to rise and more cases are identified, it may be prudent for centers to begin more intensive echocardiogram surveillance of patients who are treated with diazoxide for the evaluation of pulmonary hypertension. We propose that all infants being considered for diazoxide therapy receive echocardiograms prior to and five days after initiation of diazoxide therapy, as well as routine surveillance during the treatment course. Empiric dosing with a thiazide diuretic should also occur. Parents should be counseled about this serious, but rare, side effect so that if their child demonstrates similar symptoms or decompensates, this rare side effect could be communicated to providers who may be less familiar with diazoxide and its potential consequences.

Compliance with Ethical Standards

Conflict of interest All of the authors of this paper are employees of the United States Department of Defense, either the United States Army or United States Air Force, and have no conflicts of interest to disclose.

Ethical Approval This article does not contain any studies with human participants performed by any of the authors.

References

1. Yorifuji T (2014) Congenital hyperinsulinism: current status and future perspectives. Ann Pediatr Endocrinol Metab 19(2):57–68
2. Hussain K (2008) Diagnosis and management of hyperinsulinaemic hypoglycaemia of infancy. Horm Res 69:2–13
3. Mohamed Z, Arya VB, Hussain K (2012) Hyperinsulinaemic hypoglycaemia:genetic mechanisms, diagnosis and management. J Clin Res Pediatr Endocrinol 4:169–181
4. Arnoux JB, Verkarre V, Saint-Martin C, Montravers F, Brassier A, Valayannopoulos V et al (2011) Congenital hyperinsulinism: current trends in diagnosis and therapy. Orphanet J Rare Dis 6:63
5. Palladino AA, Bennett MJ, Stanley CA (2008) Hyperinsulinism in infancy and childhood: when an insulin level is not always enough. Clin Chem 54:256–263
6. De Leon DD, Stanley CA (2013) Determination of insulin for the diagnosis of hyperinsulinemic hypoglycemia. Best Pract Res Clin Endocrinol Metab 27:763–769
7. Arnoux JB, de Lonlay P, Ribeiro MJ, Hussain K, Blankenstein O, Mohnike K et al (2010) Congenital hyperinsulinism. Early Hum Dev 86:287–294
8. Okun R, Wilson WR, Gelfand MD (1964) The hyperglycemic effect of hypotensive drugs. J Chronic Dis 17:31–39
9. Wolff F (1964) Diazoxide hyperglycaemia and its continued relief by tolbutamide. Lancet 1:309–310
10. Coetzee WA (2013) Multiplicity of effectors of the cardioprotective agent, diazoxide. Pharmacol Ther 140(2):167–175
11. FDA Drug Safety Communication: Pulmonary Hypertension in Infants and Newborns July 2015. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm455125.htm
12. Silvani P, Camporesi A, Mandelli A, Wolfler A, Salvo I (2004) A case of severe diazoxide toxicity. Paediatr Anaesth 14(7):607–609
13. Nebesio TD, Hoover WC, Caldwell RL, Nitu ME, Eugster EA (2007) Development of pulmonary hypertension in an infant treated with diazoxide. J Pediatr Endocrinol Metab 20(8):939–944
14. Senguttuvan R, Saleh M, Wheeler M, Patel Ch, Chin C and Patel P. Diazoxide induced pulmonary hypertension in an infant. Endocrine Society's 96th Annual Meeting and Expo, Chicago, 21–24 June 2014
15. Albahri Zi Lukeš A, Mynářová K, Krylová K, Al Mawiri A, Hussain K, Neumann D (2015) Development of pulmonary hypertension in an infant treated with diazoxide for hyperinsulinism, a case report and literature review. Am J Pediatr 1(1):1–3
16. Demirel F, Unal S, Çetin II, Esen I, Arasli A (2011) Pulmonary hypertension and reopening of the ductus arteriosus in an infant treated with diazoxide. J Pediatr Endocrinol Metab 24(7–8):603–605
17. Yildizdas D, Erdem S, Küçükosmanoglu O, Yilmaz M, Yüksel B (2008) Pulmonary hypertension, heart failure and neutropenia due to diazoxide therapy. Adv Ther. 25(5):515–519
18. Sheridan BC, McIntyre RC Jr, Meldrum DR, Fullerton DA (1997) KATP channels contribute to beta- and adenosine receptor-mediated pulmonary vasorelaxation. Am J Physiol 273(5 Pt 1):L950–L956
19. Coetzee WA (2013) Multiplicity of effectors of the cardioprotective agent, Diazoxide. Pharmacol Ther 140(2):167–175
20. Klinke WP, Gilbert JAL (1980) Diazoxide in primary pulmonary hypertension. N Engl J Med 302:91–92
21. Buch J, Wennevold A (1981) Hazards of diazoxide in pulmonary hypertension. Br Heart J. 46:401–403