Reintroduction of Diazoxide after Diagnosis of Pulmonary Hypertension in a Patient with Transient Hyperinsulinism

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Abstract

Our case describes the reintroduction of diazoxide despite life-threatening pulmonary hypertension in our infant due to lack of therapeutic options for congenital hyperinsulinism.

Keywords

► congenital hyperinsulinism
► diazoxide
► pulmonary hypertension
► chlorothiazide
► side effects

Introduction

A 37-day-old 35-week premature infant with normal APGARS at birth presented to the endocrinology clinic for follow-up after being on diazoxide 13 mg/kg/day divided every 8 hours for hyperinsulinism (HI). On presentation to the clinic, a rapid response code was called as the patient appeared cyanotic and had abdominal distension and suspected necrotizing enterocolitis. He was urgently intubated for impending respiratory failure. Chest radiograph showed cardiomegaly and mild pulmonary edema. The initial echocardiogram showed a small ductus arteriosus with exclusive right-to-left shunting consistent with severely elevated (suprasystemic) pulmonary artery pressures, in addition to moderate right heart enlargement. This was in contrast to the neonatal intensive care unit (NICU) discharge echocardiogram from a month prior, where no ductus arteriosus was visualized and pulmonary pressures were estimated as only mildly elevated.

After admission, the patient remained on high ventilator settings requiring the addition of nitric oxide and had recurrent right upper lobe collapse likely from right atrial enlargement needing therapeutic bronchoscopy twice to maintain appropriate gas exchange. The patient continued to be sedated, paralyzed on mechanical ventilation, inhaled nitric oxide, diuretics, antibiotics, with multiple pulmonary hypertensive crises. The B type natriuretic peptide on admission was elevated at 2,252 picogram/milliliter (normal is <100 pg/mL) and improved to 242 pg/mL by day 5, predicted time to diazoxide elimination. He was transitioned from nitric oxide to oral sildenafl (for ongoing pulmonary vasodilation) on day 8 and extubated on pediatric intensive care unit day 18. Diazoxide was discontinued since it was thought to be the inciting agent for the development of significant pulmonary hypertension (PH), but the patient continued to need high glucose infusion rates through total parenteral nutrition to maintain normoglycemia. Since the patient was critically ill and requiring a high glucose infusion rate, and

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Discussion

Diazoxide is benzo thiadiazone derivative previously studied as an antihypertensive medication and approved by the U.S. Food and Drug Administration (FDA) for use in children and infants for a specific subset of conditions, including symptomatic hyperinsulinemic hypoglycemia and the only therapy approved by the FDA for congenital HI. Diazoxide works by activation of the ATP-sensitive potassium channels. It suppresses insulin release from the pancreatic β-cell by maintaining a hyperpolarized plasma membrane hyperpolarized.
Conclusion

Our case describes the successful reintroduction of diazoxide in an infant despite life-threatening PH, undertaken due to lack of therapeutic options for congenital HI for this patient. This was achieved using a multidisciplinary approach involving cardiology, endocrinology, and the family, and undertaken using serial echocardiographic follow-up and close clinical surveillance.

Authors’ Contributions
P.N. has made substantial contributions to the conception and design of the work; and helped in drafting the work and substantively revised it and has approved the submitted version and has agreed both to be personally accountable for the author’s own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

B.S. made substantial contributions to the conception and design of the work; and helped in drafting the work and substantively revised it and has approved the submitted version and has agreed both to be personally accountable for the author’s own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Conflict of Interest
None declared.

References
1 Silvani P, Camporesi A, Mandelli A, Wolfler A, Salvo I. A case of severe diazoxide toxicity. Paediatr Anaesth 2004;14(07):607–609
2 Welters A, Lerch C, Kummer S, et al. Long-term medical treatment in congenital hyperinsulinism: a descriptive analysis in a large cohort of patients from different clinical centers. Orphanet J Rare Dis 2015;10(01):150
3 Demirel F, Unal S, Çetin II, Esen I, Arasli A. Pulmonary hypertension and reopening of the ductus arteriosus in an infant treated with diazoxide. J Pediatr Endocrinol Metab 2011;24(7-8):603–605
4 Herrera A, Vajravelu ME, Givler S, et al. Prevalence of adverse events in children with congenital hyperinsulinism treated with diazoxide. J Clin Endocrinol Metab 2018;103(12):4365–4372
5 Nebesio TD, Hoover WC, Caldwell RL, Nitu ME, Eugster EA. Development of pulmonary hypertension in an infant treated with diazoxide. J Pediatr Endocrinol Metab 2007;20(08):939–944
6 Timlin MR, Black AB, Delaney HM, Matos RJ, Percival CS. Development of pulmonary hypertension during treatment with diazoxide: a case series and literature review. Pediatr Cardiol 2017;38(06):1247–1250
7 FDA Drug Safety Communication FDA Warns about a Serious Lung Condition in Infants and Newborns Treated with Proglycem (Diazoxide) [press release]. Food and Drug Administration. Maryland, USA: 2015
8 Thornton P, Truong I, Reynolds C, Hamby T, Nedrelow J. Rate of serious adverse events associated with diazoxide treatment of patients with hyperinsulinism. Horm Res Paediatr 2019;91(01):25–32
9 Gray KD, Dudash K, Escobar C, et al; Best Pharmaceuticals for Children Act–Pediatric Trials Network Steering Committee. Prevalence and safety of diazoxide in the neonatal intensive care unit. J Perinatol 2018;38(11):1496–1502
10 Pediatrics AAo. Postnatal glucose homeostasis in late-preterm and term infants. Pediatrics 2011;127(03):575–579
11 Silvani P, Camporesi A. Drug-induced pulmonary hypertension in newborns: a review. Curr Vasc Pharmacol 2007;5(02):129–133
12 Yildizdas D, Erdem S, Kıcıküşmanoglu O, Yılmaz M, Yüksel B. Pulmonary hypertension, heart failure and neutropenia due to diazoxide therapy. Adv Ther 2008;25(05):515–519