

# Pulmonary hypertension occurring with diazoxide use in a preterm infant with hypoglycemia

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**Abstract:** Pharmacologic modulation to open the  $K_{ATP}$  channels with diazoxide is useful in treating hyperinsulinemia. Diazoxide is being used more often in neonates with hyperinsulinemic hypoglycemia. This report highlights a case of severe pulmonary hypertension (PH) with re-opening of ductus arteriosus in an extremely premature infant after the use of diazoxide. The rapid onset of PH with respiratory failure was completely reversible. This case emphasizes the need for extreme caution with use of diazoxide in the premature infant population, especially those with chronic lung disease of prematurity. In addition, the use of diazoxide should be limited to the persistent form of congenital hyperinsulinism, after adequate work up has been completed to evaluate for other causes of hypoglycemia. It is postulated that development of PH could be related to  $K_{ATP}$  agonsim.

**Keywords:** hypoglycemia, hyperinsulinemia, pulmonary hypertension, diazoxide,  $K_{ATP}$  channels, ductus arteriosus

## Introduction

Neonatal hypoglycemia if untreated can lead to poor neurodevelopmental outcomes.<sup>1</sup> Hypoglycemia is often more difficult to treat in the presence of hyperinsulinism and diazoxide is the only drug approved by the US Food and Drug Administration (FDA) to treat hyperinsulinemic hypoglycemia.<sup>1</sup> It is generally recommended for the persistent form of this condition, which is often called the congenital hyperinsulinism-induced hypoglycemia (CHH).<sup>2</sup> The estimated incidence of CHH in the United States is 1 in 50,000 live births.<sup>3</sup> The prevalence of its use has not been well studied, but its use in neonates has increased.<sup>4</sup> Apart from diazoxide, the limited treatment options include; octreotide, long acting somatostatin analogs, sirolimus and surgery. There are several reports of diazoxide being associated with serious adverse events, which has raised concerns about the safety of this drug.<sup>4,5</sup> The development of pulmonary hypertension (PH) with its use is a known but rare adverse event and after its initiation was observed in 2.4% of patients.<sup>1</sup> This report highlights a case of severe PH with re-opening of ductus arteriosus in an extremely premature infant after treatment with Diazoxide.

## Case report

A female infant, one of di-amniotic di-chorionic twins was born at 23-week gestation to a 34-year-old, G3, P2, mother who had received prenatal care. The pregnancy was a product of in vitro fertilization. She presented in preterm labor and had a spontaneous vaginal delivery which was complicated by placental abruption. The baby had a birth weight of 460 grams. The Apgar scores were 1, 1 and 6 at 1, 5 and 10 minutes respectively. She received one dose intra-tracheal surfactant soon after birth and did not require additional doses. The initial chest radiograph revealed respiratory distress syndrome along with pulmonary

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interstitial emphysema. She was mechanically ventilated for three weeks followed by non-invasive ventilation for another five weeks. Then she needed supplemental blended nasal cannula oxygen at one liter per minute (LPM) with oxygen between 22% to 26% after that and she was also on inhaled fluticasone. The patient had medical management of a symptomatic hemodynamically significant patent ductus arteriosus from the 15th to the 17th day. Subsequently echocardiograms at 3 weeks, 9 weeks and at 14 weeks of age showed that the ductus arteriosus remained closed and there was no evidence of pulmonary hypertension. The patient received parenteral nutrition for 5 weeks till enteral feeding by orogastric and nasogastric feeding tube was fully established beyond that. At 12 weeks of age she had signs of mild cholestatic liver dysfunction and was noted to have intermittent hypoglycemia. The calories in her feeds were increased to 26 calories per ounce and her feeds had to be infused over an hour to manage that. Further workup with levels of insulin, cortisol, growth hormone, beta-hydroxy butyrate, free fatty acids, c peptide and acyl carnitine profile revealed only a mildly elevated insulin level. She had an adequate response to ACTH stimulation test but had a poor glucose response to glucagon administration. As the work up was interpreted as transient hyperinsulinism by her clinicians, she was started on diazoxide at 5 mg/kg/day with some improvement in blood glucose levels. The clinical team felt that maintaining euglycemia was essential prior to sending her home and sequentially increased the dose by 5 mg/kg till a maximum of 15 mg/kg/day was reached. At this point she remained euglycemic but her cardiorespiratory status rapidly declined. This deterioration was initially thought to be due to fluid retention and she was started on diuretics. With worsening respiratory failure and hypotension, she needed significant ventilator and inotropic support with vasopressors. She was in  $FiO_2$  of 1 and after 12 hours of conventional mechanical ventilation had to be changed to a high frequency oscillating ventilation. Her echocardiogram at 16 weeks of age (9 days after starting diazoxide) revealed pulmonary hypertension, tricuspid regurgitation (TR) with the TR jet indicating near systemic pulmonary arterial pressures, and a small ductus arteriosus with bidirectional flow. There was no evidence of right ventricular dilatation, hypertrophy or dysfunction. At this point her diazoxide was discontinued (9 days after starting). She was started on inhaled nitric oxide (iNO) at 20 ppm with prompt response in oxygenation and her  $FiO_2$  requirements. Her oxygenation index improved from 38 to 27 over 4 hours and to 19 over 24 hours. She did not receive any additional pulmonary vasodilators. She was euglycemic, when maintained on intravenous alimentation. After seven days of mechanical ventilation, when her oxygen requirements were

less than 50% her iNO was slowly weaned every six hours and she was completely off the iNO nine days after its initiation. Follow up echocardiograms showed that her pulmonary arterial hypertension resolved over two weeks and the ductus had spontaneously closed. She was again weaned off mechanical ventilation but required nasal cannula 100% oxygen at 0.2 LPM. At this point she was noted to have significant cholestasis and hepatic dysfunction. Her liver was just palpable 1–2 cms and she did not have hypertriglyceridemia or lipidemia. A genetic panel using next generation sequencing for neonatal cholestasis and alpha one antitrypsin testing were negative. Her liver function markedly worsened necessitating a referral for liver transplant at the age of six months. A liver biopsy done was inconclusive and she succumbed while waiting for the procedure at the age of eight months.

## Discussion

Diazoxide, like chlorothiazide, is a benzothiadiazine derivative and its hemodynamic effects in adults were very well described in the early 1960s.<sup>6</sup> At that time, it was presumed to be an important treatment for primary pulmonary hypertension in adults.<sup>7,8</sup> It was also noted to inhibit insulin release from the islet cells of the pancreas by selective inhibition of mitochondrial glycerol phosphate dehydrogenase.<sup>9</sup> In addition, it also causes smooth muscle relaxation and fluid retention. More recently, it has been shown to be a potential therapeutic option in ion channel diseases.<sup>10–13</sup> Opening and closing of ATP-sensitive potassium ( $K_{ATP}$ ) channels are known to affect contractility, cell adhesion, gap and tight junction regulation.<sup>10–13</sup> The  $K_{ATP}$  channels include 4 inwardly rectifying potassium ( $K_{ir}$ ) subunits and 4 sulfonylurea receptor (SUR) subunits. Pharmacologic modulation to open the  $K_{ATP}$  channels with diazoxide is useful in treating hypertension, and hyperinsulinemia, whereas  $K_{ATP}$  channel closers are used in the treatment of diabetes mellitus.<sup>10–13</sup> Most pediatric patients receiving this medication were noted to develop edema and were often started simultaneously on diuretics.<sup>4,5</sup> With increasing reports of PH developing in infants, the FDA, in 2015, issued a drug safety communication, warning of this association.<sup>14–17</sup> Other cases of severe and life threatening complications like reopening of the ductus arteriosus, sepsis syndromes, heart failure, neutropenia, thrombocytopenia, hyperuricemia and hyperosmolar coma have also been reported.<sup>1,18–22</sup> Lung biopsies done in these cases have shown a toxic vascular drug reaction.<sup>19</sup> It has been documented that PH may be more common than previously recognized in premature infants.<sup>15</sup> In infants, the incidence of PH could be higher as currently they do not routinely get echocardiogram after the initiation of the drug. The mechanism

of diazoxide-induced PH is unclear but direct toxic vascular reaction and  $K_{ATP}$  channel agonism have been postulated.<sup>19,20,23</sup> It is also possible that it could have a dose dependent effect on the PH as seen in the above case.

A small proportion of extremely preterm infants with more severe bronchopulmonary dysplasia (BPD) could over time develop PH. This case highlights the risk of development of secondary PH in infants treated with diazoxide, especially in premature infants with BPD. The sodium and fluid retention seen with its use contributes to the reopening of the ductus arteriosus and worsening any pre-existing PH. Even though it is reversible after cessation of therapy, PH is a life threatening complication. The etiology of cholestatic liver dysfunction is unclear as the testing was inconclusive and probably unrelated to the use of diazoxide. The significant deterioration in clinical status after its use might not have helped its resolution. This case is unique in that the patient had serial echocardiography done, as the patient's ductus arteriosus was being monitored and the patient had echocardiography soon after initiation of treatment. Even though she was extremely preterm, she had mild evolving chronic lung disease (CLD), as her  $FiO_2$  requirements were low and she did not have any documented prior evidence of PH. In addition, this adds to the body of evidence on the number of patients developing PH, which would advocate against indiscriminate use of this drug. Extreme caution must be exercised in the very low birth weight infant and in extremely premature infants, who are at higher risk for development of PH secondary to CLD and its use should be limited to the persistent form of CHH. If diazoxide therapy is initiated, then serial echocardiography should be performed in this high risk patient population of premature infants.

## Ethics statement

Written informed consent for publication has been obtained from infant's parent. Institutional ethics and research review board has provided a waiver from the committee's full review and approval for the case report.

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## Disclosure

The author reports no conflicts of interest in this work.

## References

- 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.
- Banerjee I, Salomon-Estebanez M, Shah P, Nicholson J, Cosgrove KE, Dunne MJ. Therapies and outcomes of congenital hyperinsulinism-induced hypoglycaemia. *Diabet Med.* 2019;36(1):9–21.
- De Leon DD, Stanley CA. Congenital hypoglycemia disorders: new aspects of etiology, diagnosis, treatment and outcomes: highlights of the proceedings of the congenital hypoglycemia disorders symposium, Philadelphia April 2016. *Pediatr Diabet.* 2017;18(1):3–9.
- Gray kD, Dudash K, Escobar K, Freel 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.
- Timlin MR, Black AB, Delaney HM, Matos RI, Percival CS. Development of pulmonary hypertension during treatment with diazoxide: a case series and literature review. *Pediatr Cardiol.* 2017;38(6):1247–1250.
- Rowe GG, Leicht TR, Boake WC, Kyle JC, Crumpton CW. The systemic and coronary hemodynamic effects of diazoxide. *Am Heart J.* 1963;66:636–643.
- Wang SW, Pohl JE, Rowlands DJ, Wade EG. Diazoxide in treatment of primary pulmonary hypertension. *Br Heart J.* 1978;40(5):572–574.
- Klinke WP, Gilbert JA. Diazoxide in primary pulmonary hypertension. *N Engl J Med.* 1980;302(2):91–92.
- Macdonald MJ. High content of mitochondrial glycerol-3-phosphate dehydrogenase in pancreatic islets and its inhibition by diazoxide. *J Biol Chem.* 1981;256(16):8287–8290.
- Lawson K. Potassium channel openers as potential therapeutic weapons in ion channel disease. *Kidney Int.* 2000;57(3):838–845.
- Jahangir A, Terzic A.  $K(ATP)$  channel therapeutics at the bedside. *J Mol Cell Cardiol.* 2005;39(1):99–112.
- Kharade SV, Nichols C, Denton JS. The shifting landscape of  $KATP$  channelopathies and the need for 'sharper' therapeutics. *Future Med Chem.* 2016;8(7):789–802.
- Rubaiy HN. The therapeutic agents that target ATP-sensitive potassium channels. *Acta Pharm.* 2016;66(1):23–34.
- Silvani P, Camporesi A, Mandelli A, Wolfer A, Salvo I. A case of severe diazoxide toxicity. *Paediatr Anaesth.* 2004;14(7):607–609.
- Silvani P, Camporesi A. Drug-induced pulmonary hypertension in newborns: a review. *Curr Vasc Pharmacol.* 2007;5(2):129–133.
- US Food and Drug Administration. FDA Drug Safety Communication (FDA webpage): FDA warns about a serious lung condition in infants and newborns treated with Proglycem (diazoxide). Available from: <https://www.fda.gov/Drugs/DrugSafety/ucm454833.htm>. Accessed December 3, 2018.
- US Food and Drug Administration. Drug Safety communications (FDA webpage download): FDA warns about a serious lung condition in infants and newborns treated with Proglycem (diazoxide). Available from: <https://www.fda.gov/downloads/Drugs/DrugSafety/UCM454863.pdf>. Accessed December 3, 2018.
- 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.
- 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(8):939–944.
- Yildizdas D, Erdem S, Küçükosmanoğlu O, Yılmaz M, Yüksel B. Pulmonary hypertension, heart failure and neutropenia due to diazoxide therapy. *Adv Ther.* 2008;25(5):515–519.
- Gerardin M, Denizot S, Texier R, et al. Pulmonary hypertension in newborns treated with diazoxide: about two cases. *Fundam Clin Pharm.* 2010;24(s1):81.
- Mangla P, Hussain K, Ellard S, Flanagan SE, Bhatia V. Diazoxide toxicity in a child with persistent hyperinsulinemic hypoglycemia of infancy: mixed hyperglycemic hyperosmolar coma and ketoacidosis. *J Pediatr Endocrinol Metab.* 2018;31(8):943–945.
- Wang T, Zhang ZX, Xu YJ. Effect of mitochondrial  $KATP$  channel on voltage-gated  $K^+$  channel in 24 hour-hypoxic human pulmonary artery smooth muscle cells. *Chin Med J.* 2005;118(1):12–19.

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