

## CASE REPORT

# Reversible Pulmonary Hypertension in an Infant Treated with Diazoxide

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### Abstract

**Background:** Diazoxide is the main therapeutic agent for congenital hyperinsulinism. The drug is generally well tolerated; however, in this report severe adverse effects including heart failure (HF) and pulmonary hypertension (PH) in an infant are reported.

**Case report:** A sixteen-day male infant with persistent hypoglycemia and with diagnosis of congenital hyperinsulinism underwent near total pancreatectomy. Despite surgery, hypoglycemia persisted, and thus oral diazoxide 5 mg/kg/dose three times per day was administered. At four months of age, the patient was again admitted to the hospital because of respiratory distress and poor feeding from a week earlier. On physical examination, he was tachypneic and mild intercostal retraction was present. Tachycardia existed without definitive murmur. Moderate hepatomegaly was detected. Chest X-ray revealed cardiomegaly. Echocardiography showed right atrial and ventricular dilatation, and pulmonary pressure of 70 mmHg. In the next day, respiratory failure developed and so the patient was intubated and mechanically ventilated. Diazoxide was discontinued and 10% dextrose water (DW) was initiated. Four days later, the patient was extubated. Blood glucose remained in normal limit. Gradually the concentration of DW was decreased. The patient was discharged and followed up without any medication. Echocardiogram in one month later showed normal heart dimension and reduction of pulmonary pressure to 20 mmHg, and resolution of right atrial and ventricular enlargement.

**Discussion:** Diazoxide reduces peripheral vascular resistance and blood pressure as the result of direct vasodilatory effect on smooth muscles in peripheral arterioles. It causes sodium and water retention and decrease of urinary output which can result in expansion of plasma and extracellular fluid volume, and consequently edema and congestive cardiac failure.

**Conclusion:** Diazoxide therapy for infants with congenital hyperinsulinism is associated with the threat of PH and HF. Periodic echocardiography may be helpful for the infants under long term diazoxide therapy.

**Keywords:** Diazoxide; Heart Failure; Infant; Pulmonary Hypertension; Toxicity

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### INTRODUCTION

Congenital hyperinsulinism, formerly termed nesidioblastosis, is the most common cause of hypoglycemia in a newborn (1). Diazoxide, a benzothiadiazine derivative with an inhibitory effect on insulin secretion, is the main therapeutic agent for this disorder (1). The most frequent side effect of diazoxide is hypertrichosis that can be reversed by drug discontinuation (2,3). In addition, severe adverse effects such as heart failure (HF), pulmonary hypertension (PH), neutropenia and acute renal failure following diazoxide therapy have rarely been reported, so far (4-7). In this case report a four-month infant with congenital hyperinsulinism is presented who developed PH and cardiorespiratory failure during diazoxide therapy.

### CASE REPORT

A two-day male neonate was referred to the neonatal intensive care unit of Imam Khomeini Hospital, Ahvaz, Iran because of hypoglycemia resistant to ordinary

rate of glucose infusion, apnea and cyanosis. He was born by cesarean section delivery with birth body weight of 5 kg. There was a history of sibling death at 2 days of life for unexplained reasons. On physical examination, the patient was large for gestational age without observable congenital anomalies. Laboratory tests revealed hypoglycemia. The patient was treated with dextrose water (DW) up to 18% concentration through an umbilical vein catheter.

Because of persistent hypoglycemia; diazoxide, octerotide and glucagon was tried. Despite aggressive medical treatment, frequent episodes of hypoglycemia detected. The patient experienced no episode of seizure during admission. Serum insulin, C-peptide, cortisol and growth hormone were reported normal. With diagnosis of congenital hyperinsulinism, near total pancreatectomy (95%) was performed in the sixteenth day of life of the neonate. Pathologic assessments confirmed the diagnosis.

Despite surgery, hypoglycemia persisted and thus oral

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diazoxide 5 mg/kg/dose three times per day was administered. The patient was discharged with diazoxide and instruction for control of arterial blood glucose. At follow-up visits, blood glucose remained at lower limit of normal, and thus the drug was continued. At four months of age, the patient was again admitted to the hospital because of respiratory distress and poor feeding from a week earlier. On physical examination, his weight was 6.53 kg. His respiratory rate was 70 breaths per minute and mild intercostal retraction was present. On auscultation of chest, generalized wheezing was heard. The heart was hyperkinetic and tachycardia existed without definitive murmur. Moderate hepatomegaly was detected. Chest X-ray revealed cardiomegaly (Figure 1A). Echocardiography showed right atrial and ventricular dilatation and pulmonary pressure of 70 mmHg. In the second day of admission, respiratory failure developed and so the patient was intubated and mechanically ventilated.

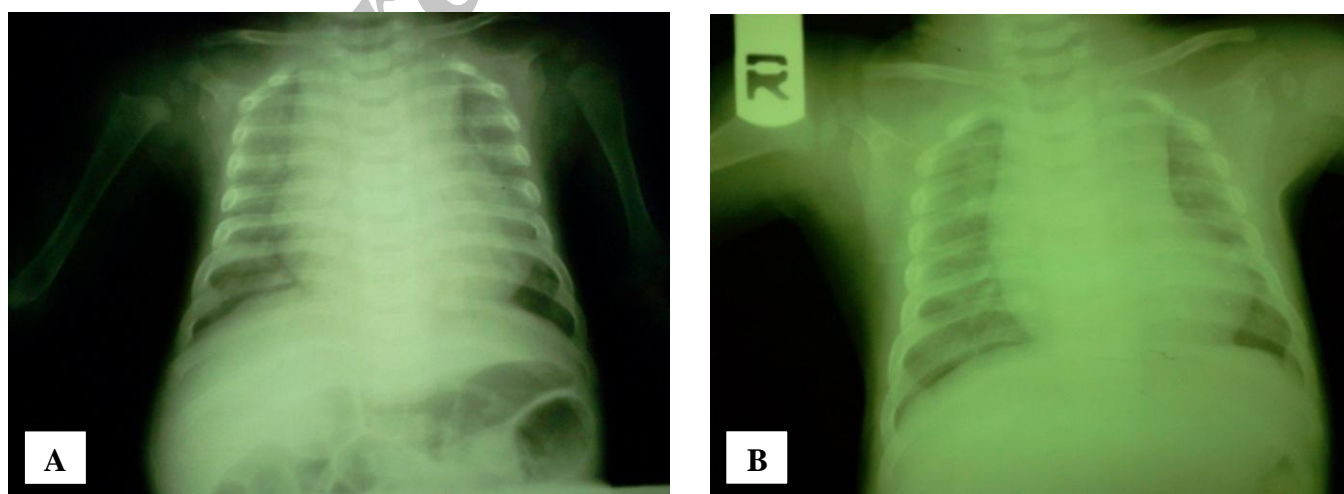
Diazoxide was discontinued and 10% DW was initiated. Four days later, the patient was extubated. Blood glucose remained in normal limit. The concentration of DW gradually tapered off and with tolerance of full oral feeding, intravenous fluid was discontinued. The patient was discharged and followed up without any medication. At follow-up, the blood glucose remained normal. Chest X-ray (Figure 1B) and echocardiogram in one month later showed normal heart dimension and reduction of pulmonary pressure to 20 mmHg, and resolution of right atrial and ventricular enlargement.

## DISCUSSION

Congenital hyperinsulinism is a general term that is used to explain the various etiologies for neonatal hyperinsulinemic hypoglycemia. This disorder usually presents during the first 24 to 48 hours of birth with symptoms such as seizure, hypotonia, apnea, cyanosis and severe hypoglycemia (1). Conservative management and

inhibition of insulin secretion with diazoxide and somatostatin has shown to be ineffective unless subtotal (85%) or total (95%) pancreatectomy is performed (8,9). If hypoglycemia persists post-surgery, diazoxide should be administered for the patients.

Apart from common side effects of diazoxide, rare severe adverse effects such as HF and PH have been observed (4-7). Although infants with congenital hyperinsulinism are usually treated with other medications in addition to diazoxide (e.g. octerotide), Silvani et al. reported resolution of PH and HF in a neonate after withdrawal of diazoxide, while octerotide was continued (4). Diazoxide reduces peripheral vascular resistance and blood pressure as the result of direct vasodilatory effect on smooth muscles in peripheral arterioles. It causes sodium and water retention and decrease of urinary output which can result in expansion of plasma and extracellular fluid volume, and consequently edema and congestive cardiac failure (3-7). The mechanism of PH due to diazoxide toxicity is still unclear. The cause of diazoxide-induced pulmonary artery hypertension has been attributed to the ATP-sensitive channel agonism of diazoxide. Toxic effects of this drug result in fluid retention, congestive HF, pulmonary artery smooth muscle hypertrophy and PH (10). Diazoxide also opens mitochondrial ATP-sensitive potassium channels and causes release of excessive cytochrome C and overproduction of hydrogen peroxide leading to PH. These effects abruptly subside after diazoxide discontinuation (10,11). Demirel et al. proposed that the mentioned mechanism might be the cause of re-opening of ductus arteriosus in their case who was treated with diazoxide for congenital hyperinsulinism (7). Yildizdas et al. suggested that the direct toxic effect of diazoxide on the pulmonary artery, myocardium and bone marrow might be responsible for PH, HF and neutropenia in a four-month girl (6). Similarly, Nebesio et al. showed that lung biopsy of a newborn with PH due to diazoxide toxicity was suggestive of toxic vascular drug reactions (5).



**Figure 1.** Chest X-ray of the patient: A) on admission showing moderate cardiomegaly, B) one month post-discharge showing normal heart size

In all reported cases of diazoxide-induced PH and HF, the drug was discontinued 6 to 13 days after admission. In the present case, diazoxide was discontinued in the second day of admission. Early discontinuation of diazoxide led to rapid recovery of respiratory and heart failure and gradual reduction of pulmonary artery pressure. Based on the present case and previously published reports (4-7), periodic echocardiography with regular intervals is recommended for infants who are under long term treatment of diazoxide.

### CONCLUSION

Diazoxide therapy for infants with congenital hyperinsulinism is associated with the threat of PH and HF. Periodic echocardiography may be helpful for the infants under long term diazoxide therapy.

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