CASE REPORT

Pulmonary Hypertension Following Increased Dosing of Diazoxide in an Infant

Yuji Ohnishi, MD, Seigo Okada, MD, Hiroki Yasudo, MD, Sasagu Kimura, MD, Yasuo Suzuki, MD and Shunji Hasegawa, MD

Summary

Diazoxide, a drug used to treat hyperinsulinemic hypoglycemia (HH), is associated with pulmonary hypertension (PH), as reported by the US Food and Drug Administration. However, no report has detailed the association between diazoxide dose and PH development. We report a case of an infant with HH, subsequently complicated by diazoxide-induced PH. When diazoxide was introduced, PH did not appear initially, but it developed during increased dosing. We monitored PH via regular echocardiography examinations. PH gradually improved with tapering of the diazoxide dose and disappeared after drug discontinuation. Our case suggests a diazoxide dose threshold might induce PH. Therefore, close echocardiography examinations should accompany diazoxide treatment.

(Int Heart J 2020; 61: 1084-1087)

Key words: Adverse effect, Echocardiography, Potassium ion channel, Hyperinsulinemic hyperglycemia, Ventricular pressure

Diazoxide is a first-line agent for hyperinsulinemic hypoglycemia (HH) in neonates. As a specific adenosine triphosphate-sensitive potassium ion channel (KATP channel) agonist, it inhibits insulin secretion from pancreatic beta cells by promoting the opening of ATP-sensitive K+ channels but reducing that of Ca2+ channels.

Although diazoxide treatment has favorable clinical outcomes for HH, there are reports of some serious adverse events, such as pulmonary hypertension (PH), related to its use (Table). The US Food and Drug Administration issued a drug safety communication warning that PH could be associated with diazoxide. It remains unclear whether the severity of diazoxide-induced PH depends on dosage, starting from a threshold. Two studies reported echocardiography showed no PH after initiating diazoxide. Apart from those two, no study reported monitoring PH variation induced by diazoxide during the dose change via repetitive echocardiogram examinations.

Herein, we report an infant with Beckwith-Wiedemann Syndrome (BWS), treated with diazoxide for HH. PH developed as right ventricular pressure increased on echocardiography during increased dosing, but it was not detected immediately after initiating diazoxide treatment. Right ventricular pressure gradually decreased with a decrease in diazoxide dose and returned to normal after drug cessation. Careful echocardiography monitoring may permit the early detection of PH.

Case Report

A Japanese male infant was born at 37 weeks of gestation. His birth weight and height were 4,108 g (+4.0 standard deviation [SD]) and 54.5 cm (+4.2 SD), respectively, with Apgar scores at 1 and 5 minute(s) of 6 and 7, respectively. He had macroglossia, macrosomia, hepatomegaly, and nephromegaly, suggesting BWS. He was admitted to our neonatal intensive care unit (NICU). The epigenetic analysis showed hypermethylation in the differentially methylated region of H19, related to BWS. After the 22nd day of life (DOL), the patient developed persistent hypoglycemia (serum glucose level was 47 mg/dL). A laboratory examination demonstrated serum insulin levels of 2.9 μIU/mL (rr [reference range]: < 1), serum 3-hydroxybutyric acid levels of 0.234 mmol/L (rr: > 2.0), and serum-free fatty acid levels of 0.19 mmol/L (rr: > 1.5). These results prompted us to start diazoxide at an initial dose of 5.2 mg/(kg ⋅ day) on DOL 30. Diazoxide was gradually increased up to 10.4 mg/(kg ⋅ day) based on his blood glucose level. The patient recovered from hypoglycemia and was discharged on DOL 69. His echocardiography, at the point of discharge and one month later, showed no evidence of PH. Following hypoglycemia recurrence after discharge, diazoxide was gradually increased to 11.5 mg/(kg ⋅ day) in an outpatient clinic on DOL 75 (Figure 1).

Two months after discharge, the infant showed mild...
respiratory distress and poor sucking. Echocardiography revealed an increase in the estimated right ventricular pressure of 63 mmHg (systolic blood pressure was 104 mmHg [pulmonary/systemic pressure ratio 0.60]). After 2 weeks, he was hospitalized again for further examinations. We increased the diazoxide dosage to 12.9 mg/(kg day) at rehospitalization. The percutaneous oxygen saturation was 93%-95% under room air conditions. No abnormal breath sounds were audible during the waking state. A grade 2 systolic regurgitant murmur was audible at the fourth left sternal border. The blood test revealed elevated plasma levels of brain natriuretic peptide (BNP), at 268 pg/mL (rr: < 18), and human atrial natriuretic peptide (HANP), at 273 pg/mL (rr: < 43). The patient tested negative for hepatitis B, hepatitis C, and human immunodeficiency virus. Chest radiography revealed cardiomegaly, with a cardiothoracic ratio of 0.61. Twelve-leads electrocardiography (ECG) showed sinus rhythm, right-axis deviation, a tall P wave in the II-lead, and positive T waves in leads V1 to V6. Echocardiography showed moderate tricuspid regurgitation (TR) and a D-shaped left ventricle (Figure 2A). The estimated right ventricular pressure was 75 mmHg (systolic blood pressure was 89 mmHg [pulmonary/systemic pressure ratio 0.84]). Lung perfusion scintigraphy did not show any wedge-shaped blood flow defect. In cardiac catheterization, the mean main pulmonary artery (MPA) pressure and pulmonary vascular resistance (Rp) were remarkably elevated to 58 mmHg and 6.6 Wood units · m⁻², respectively. The left pulmonary artery wedge pressure, right pulmonary artery wedge pressure

---

Table. Case Reports Related to Diazoxide-Induced PH

| Author         | Journal               | Year | Age | Sex | Dose at PH onset (mg/ (kg·day)) | Time from the initiation to PH onset (day) | Severity       | Result         | Time from diazoxide cessation to disease recovery (days) | Underlying condition                  |
|----------------|-----------------------|------|-----|-----|---------------------------------|-------------------------------------------|----------------|----------------|--------------------------------------------------------|---------------------------------------|
| Silvani, et al. | Paediatr Anaesth      | 2004 | 43  | M   | 17                              | 0                                         | Unknown        | Recuperation   | 5                                                      | Premature infant                      |
| Nebesio, et al. | J Pediatr Endocrinol  | 2007 | 43  | F   | 13                              | 9                                         | Severe         | Recuperation   | Within 6 weeks                                       | Laryngomalacia and obstructive apnea |
| Yildizdas D    | Adv Ther Endocrinol   | 2008 | 4 months | F | 15                              | 10                                        | Severe         | Recuperation   | 3                                                      | Premature infant                      |
| Demirel, et al.| J Pediatr Endocrinol  | 2011 | 6 days | M | 15                              | 4                                         | Moderate       | Recuperation   | 1                                                      | None                                  |
| Timlin, et al. | Pediatr Cardiol       | 2017 | 29 days | M | 13                              | 28                                        | Severe         | Recuperation   | 6                                                      | Premature infant                      |
| Timlin, et al. | Pediatr Cardiol       | 2017 | 5 days | M | 12                              | 3                                         | Severe         | Recuperation   | 40                                                     | Beckwith-Wiedemann Syndrome           |
| Timlin, et al. | Pediatr Cardiol       | 2017 | 12 weeks | M | Not described                   | 71                                        | Severe         | Recuperation   | 1                                                      | Premature infant and small for gestational age |
| Kylat RI       | Drug Healthc Patient Saf | 2019 | 16 weeks | F | 15                              | 9                                         | Severe         | Recuperation   | > 2 weeks                                              | Extremely premature and low birth weight infant |
| Our case       |                       | 20 weeks | 11.5 | M | 103                             | Moderate-severe                             | Recuperation   | 1                                                      | Beckwith-Wiedemann Syndrome           |

**Figure 1.** The relationship between the dosage of diazoxide and estimated pulmonary/systemic pressure ratio. The estimated pulmonary/systemic pressure ratio is calculated by echocardiography. DOL indicates the day of life.
and left ventricular end-diastolic pressure were also elevated to 19, 18, and 18 mmHg, respectively. The partial pressures of oxygen and carbon dioxide in the arterial blood were 128 mmHg and 50.0 mmHg, respectively. Both mean MPA pressure and Rp were decreased to 45 mmHg and 2.3 Wood Units · m², respectively, in the vasoreactivity challenge test, by high-concentration oxygen inhalation. After the catheter examination, we started oxygen inhalation therapy along with diuretics and sildenafil. Estimated right ventricular pressure and pulmonary/systemic pressure ratio were slightly reduced but not restored. We suspected diazoxide-associated PH, so we decreased the dose of diazoxide. We discontinued it 30 days post-hospitalization since the blood glucose level was well controlled; hypoglycemia did not relapse. The levels of BNP and HANP decreased to 16.9 pg/mL, and 125 pg/mL, respectively. The ECG findings representing PH improved. Echocardiography showed mild TR and a round-shaped left ventricle (Figure 2B). Estimated right ventricular pressure was 39 mmHg (systolic blood pressure was 96 mmHg [pulmonary/systemic pressure ratio 0.40]) Although oxygenation, sildenafil, and diuretics were successively withdrawn, PH and HH did not increase. Forty-eight days post-hospitalization, the estimated right ventricular pressure returned to normal levels, the BNP was 4.0 ng/mL, and the patient was discharged. Four months following discharge, cardiac catheterization revealed a mean MPA pressure of 21 mmHg and an Rp of 0.9 Wood units · m². Left pulmonary artery wedge pressure, right pulmonary artery wedge pressure and left ventricular end-diastolic pressure also improved to 12, 10, and 12, respectively. The infant has not shown any PH recurrence so far.

**Discussion**

To the best of our knowledge, this is the first case report of PH possibly induced by an increased diazoxide dosage and improved by dose reduction. PH was evaluated by echocardiography at regular intervals. We first introduced diuretics and sildenafil to treat PH. After that, the estimated pulmonary/systemic pressure ratio dropped slightly but restored. Hence, we concluded that a combination of diuretics and sildenafil treatment had limited efficacy against PH. Also, PH was primarily due to a diazoxide adverse effect since it developed after increased diazoxide dosing, improved with reduction, and finally disappeared after diazoxide withdrawal. In some reports, diazoxide-induced PH exhibited a sudden onset after a high dosage or after a dose increase, similar to our case. However, previous cases did not describe the relationship between the dosage of diazoxide and PH severity, based on an echocardiographic evaluation.

Previous reports indicated that the time from diazoxide initiation to the onset of PH ranges from 3 to 71 days (Table). In our case, it took 103 days for PH to develop, possibly because of how rapidly the treatment dose increased. In our case, diazoxide dose was increased to 11.5 mg/(kg · day) 50 days after drug initiation. In contrast, the doses were increased to 12-17 mg/(kg · day) within 28 days after drug initiation in previous studies except for the case that did not consider treatment dose. The diazoxide dose was 10.4 mg/(kg · day) when the infant was discharged from the NICU; no symptoms pointed toward PH during the physical examination and echocardiography, performed at an outpatient clinic. PH developed when diazoxide was increased to 11.5 mg/
(kg · day) and gradually improved with diazoxide dose reduction. Echocardiography revealed that estimated right ventricular pressure and pulmonary/systemic pressure ratio increased during the increased dosing of the medication, decreased with tapering, and returned to normal levels after drug cessation (Figure 1). This suggests a diazoxide dose threshold for PH induction was between 10.4 and 11.5 mg/(kg · day), and its severity depended on the diazoxide dose and was reversible. Previous studies had reported that diazoxide dose exceeded 12 mg/(kg · day) in most cases when PH developed, which were in line with our results (Table). Moreover, the patients recovered from PH immediately after the withdrawal of diazoxide. Diazoxide has a short half-life of 9.5 to 24 hours when it is applied to pediatric patients. We speculate that diazoxide toxicity is more influenced by the dose rather than the administration duration and that PH induced by diazoxide develops at a certain dose, possibly between 10.4 and 11.5 mg/(kg · day), in general.

The mechanisms underlying diazoxide’s induction of PH remain unknown. One hypothesis is that diazoxide, as a KATP channel agonist, depolarizes the mitochondrial membrane potential by opening the mitochondrial KATP channel, followed by cytochrome C release, mitochondrial hydrogen peroxide overproduction, and increased proliferation and decreased apoptosis of human pulmonary artery smooth muscle cells. According to a previous study using PH model rats, it took 3 weeks for rats to develop severe PH followed by thickening of pulmonary artery media concomitantly with the proliferation of smooth muscle cells. In our case, it had already been more than 3 weeks prior to the development of PH after increasing the diazoxide dose to 11.5 mg/kg · day. However, the duration from diazoxide discontinuation to PH improvement might not have been sufficient for smooth muscle apoptosis in the present case. From this point of view, excessive vasoconstriction or NO production might be involved in PH pathogenesis. Moreover, elevated left ventricular end-diastolic pressure was restored after diazoxide discontinuation. Previously, serious adverse events associated with diazoxide use, including heart failure, have been reported. Hence, post-capillary PH due to left ventricular diastolic dysfunction might have also been involved in the pathogenesis of PH.

In conclusion, our case suggests that there might be a dose threshold for PH induced by diazoxide treatment. Since diazoxide is commonly used for infants with HH, careful follow-up with echocardiography is required to monitor PH development during diazoxide treatment.

Disclosure
Conflicts of interest: None.
Informed Consent: Written informed consent was obtained from the patient’s parents for publication of this case report.

References
1. Yildizdas D, Erdem S, Kucukosmanoglu O, Yilmaz M, Yuksel B. Pulmonary hypertension, heart failure and neutropenia due to diazoxide therapy. Adv Ther 2008; 25: 515-9.
2. Hansen JB. Towards selective Kir6.2/SUR1 potassium channel openers, medicinal chemistry and therapeutic perspectives. Curr Med Chem 2006; 13: 361-76.
3. Silvani P, Camporese A, Mandelli A, Wolffer A, Salvo I. A case of severe diazoxide toxicity. Pediatr Anesth 2004; 14: 607-9.
4. 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: 939-44.
5. Demirel F, Unal S, Cetin II, Ercan I, Arasli A. Pulmonary hypertension and reopening of the ductus arteriosus in an infant treated with diazoxide. J Pediatr Endocrinol Metab 2011; 24: 603-5.
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: 1247-50.
7. Kylat RI. Pulmonary hypertension occurring with diazoxide use in a preterm infant with hypoglycemia. Drug Healthc Patient Saf 2019; 11: 7-10.
8. Food and Drug Administration. FDA Drug Safety Communication. FDA warns about serious lung condition in infants and newborns treated with Proglycem (diazoxide). Available at: http://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-about-serious-lung-condition-infant-s-and-newborns-treated. Accessed December 26, 2019.
9. Pruitt AW, Dayton PG, Patterson JH. Disposition of diazoxide in children. Clin Pharmacol Ther 1973; 14: 73-82.
10. Hu HL, Zhang ZX, Chen CS, Cai C, Zhao JP, Wang X. Effects of mitochondrial potassium channel and membrane potential on hypoxic human pulmonary artery smooth muscle cells. Am J Respir Cell Mol Biol 2010; 42: 661-6.
11. Taraseviciene-Stewart L, Kasahara Y, Alger L, et al. Inhibition of the VEGF receptor 2 combined with chronic hypoxia causes cell death-dependent pulmonary endothelial cell proliferation and severe pulmonary hypertension. FASEB J 2001; 15: 27-38.
12. Yuan JX, Aldinger AM, Juhaszova M, et al. Dysfunctional voltage-gated K+ channels in pulmonary artery smooth muscle cells of patients with primary pulmonary hypertension. Circulation 1998; 98: 1400-6.
13. Giaid A, Saleh D. Reduced expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension. N Engl J Med 1995; 333: 214-21.
14. Fukutomi M, Shimodera M, Maeda Y, Ikawara M, Hara M. Safety and effectiveness, including intelligence prognosis, of diazoxide in pediatric patients with hyperinsulinemic hypoglycemia: Special survey in Japan (long-term, all-case survey). Clin Pediatr Endocrinol 2018; 27: 131-45.