

Hyperosmolar hyperglycemic syndrome induced by diazoxide and furosemide in a 5-year-old girl

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Abstract. Hyperglycemia and hyperosmolar hyperglycemic syndrome (HHS) are the rare adverse effects of diazoxide. Furosemide has been reported to worsen glucose tolerance and cause HHS. A 5-yr-old girl presented to the emergency department with complaints of tachycardia, polyuria, and lethargy for 1 wk prior to hospitalization. She was treated with two diuretics for aortic valve reflux disease and diazoxide for congenital hyperinsulinemia. She was diagnosed with HHS based on her serum glucose level of 529 mg/dL and serum osmotic pressure of 357 mOsm/kg. There were no findings suggestive of new-onset diabetes mellitus. She had fever on admission and, was diagnosed with a urinary tract infection. The blood diazoxide level at the time of hospitalization was 25 µg/dL. Diazoxide use, even in patients with low diazoxide levels, may cause hyperglycemia. Patients on diuretics and diazoxide must be carefully monitored, considering the risk of developing HHS.

Key words: Hyperosmolar hyperglycemic syndrome, diazoxide, furosemide, congenital hyperinsulinemia

Introduction

Hyperosmolar hyperglycemic syndrome (HHS) can lead to serious hyperglycemia due to relative insulin deficiency and increased secretion of counterregulatory hormones, such as glucagon, catecholamine, and growth hormone, as well as severe dehydration and electrolyte abnormalities (hyperosmolarity) due to osmotic diuresis (1). Although HHS is rare in children, it has a high mortality rate and requires intensive care unit treatment (1). Diazoxide treatment for hyperinsulinemia can lead to the onset of hyperglycemia or HHS as a serious adverse effect (3–6). We herein report a case of HHS induced by concomitant use of diazoxide and diuretics, despite a low blood diazoxide level.

Case Presentation

A 5-yr-old girl with Cornelia de Lange syndrome was treated with diazoxide therapy (5 mg/kg per d) for congenital hyperinsulinemia (CHI). She was also taking furosemide (1 mg/kg per d) and spironolactone (1 mg/kg per d) for the aortic bicuspid valve and aortic regurgitation. She was on prophylactic antibiotics because she had grade 3 left vesicoureteral reflux disease. She also underwent tracheostomy and brachiocephalic artery transection for laryngomalacia and tracheomalacia. She

had no family history of diabetes mellitus. She started taking enalapril maleic acid (0.1 mg/kg per d) after consultation with a cardiovascular outpatient clinic 2 wk before hospitalization.

She experienced tachycardia and polyuria 1 wk prior to hospitalization. She had a fever (body temperature, 37.7°C) a day before hospitalization. Her blood test showed a C-reactive protein of 9.8 mg/dL; hence, she was administered tosylflouxacin. On the day of hospitalization, she was lethargic and admitted to the pediatric intensive care unit. Blood investigations revealed hyperglycemia and hypernatremia.

At the time of hospitalization, the height and weight of the patient were 92.5 cm and 13.8 kg, respectively. Her body weight prior to illness was 14.7 kg, implying a 7% reduction. Her body temperature was 37.0°C, heart rate was 170 beats/min, blood pressure was 107/59 mmHg, and respiratory rate was 25/min. Consciousness was impaired (Glasgow Coma Scale [GCS], E3VTM4). Physical examination revealed dry mouth, bilateral air entry into the chest, no rales, clear heart sounds (not exaggerated), full and soft abdomen without tenderness, no hepatomegaly, and a capillary refill time of 2 sec. She was diagnosed with hypovolemic shock based on impaired consciousness, tachycardia, and dehydration.

Blood investigations revealed hyperglycemia, hyperosmolarity, acute renal dysfunction, and

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Table 1. Laboratory data on admission

CBC		Atrial blood gas		Urine test	
WBC	12900 / μ L	pH	7.413	Protein	(2+)
Hb	12.6 mg/dL	pCO ₂	51 mmHg	Ketone	(-)
Hct	42.8 %	HCO ₃ ⁻	31.9 mEq/L	Occult blood	(2+)
Plt	28.1 \times 10 / μ L	BE	6 mEq/L	Urobilinogen	(\pm)
		Lac	1.5 mmol/L	Bilirubin	(-)
		Na	157.7 mEq/L	WBC	30–49/HPF
		K	4.33 mEq/L	RBC	10–19/HPF
		Cl	122 mEq/L		
		AG	8 mmol/L		
Biochemical test				Culture	
TP	6.7 g/dL	Plasma glucose	529 mg/dL	Urine culture	<i>E. coli</i> 10*4
Alb	3.6 g/dL	HbA1c (NGSP)	5.8 %	Sputum culture	negative
AST	109 IU/L	3-hydroxyacetic acid	0.1 μ mol/L	Blood culture	negative
ALT	142 IU/L	Insulin	11.6 μ U/mL		
LDH	330 IU/L	C-peptide	5.13 ng/mL		
T-Bil	0.15 mg/dL	ACTH	38 pg/mL		
CK	11 IU/L	IGF1	8 ng/mL	Serum concentration	
BUN	41.3 mg/dL	Plasma cortisol	32.8 μ g/dL	diazoxide	25 μ g/mL
Cre	0.39 mg/dL	GH	0.7 ng/mL		
Na	160 mEq/L	TSH	3.011 μ IU/mL		
K	4.5 mEq/L	fT3	2.24 pg/mL		
Cl	120 mEq/L	fT4	0.66 ng/dL		
Ca	9.2 mEq/L	Anti IA2 antibody	< 0.6 U/mL		
P	2.9 mEq/L	Anti GAD antibody	< 5.0 U/mL		
Tchol	190 mg/dL	Anti insulin antibody	< 0.4 U/mL		
TG	321 mg/dL				
CRP	9.56 mg/dL	Serum osmolality	357 osm/kg		
Lipase	23 mg/dL				
Amylase	33 U/L				

hypernatremia associated with intravascular dehydration, with a blood glucose level of 529 mg/dL and serum osmotic pressure of 357 mOsm/kg (Table 1). Based on the above findings, the patient was diagnosed with HHS. Intensive investigation was continued during treatment to determine the etiology.

Pulse rate (140 beats/min) and consciousness level (GCS, E4V7M5) improved after the peripheral venous route was secured and intravenous extracellular fluid (20 mL/kg) was administered. Diazoxide was stopped, and fluid infusion was continued at a rate of 8 mL/kg/h. Her blood glucose level improved to 185 mg/dL 3 h after hospitalization. The infusion was changed to a maintenance fluid with a glucose level of 9.6% (glucose infusion rate, 6.8 mg/kg/min). The blood glucose and electrolyte levels were corrected. Insulin was not administered because of coexisting hyperinsulinemia and rapid improvement of blood glucose levels with fluid replacement alone.

Blood investigations revealed an increased inflammatory response (white blood cell count, 12,900/

μ L; C-reactive protein, 9.62 mg/dL) along with an infection (Table 1). The patient had a history of artificial bloodstream infection, and urinary tract infection. She was then administered cefepime. Chest X-ray was normal. Her blood amylase, lipase, and creatinine kinase levels were normal. Anti-GAD, IA2, and anti-insulin antibodies were negative. The HbA1c was 5.8%, and the blood C-peptide level was 5.13 mg/dL. *Escherichia coli* was detected in urine culture. She was diagnosed with breakthrough urinary tract infection because a single bacterial species was detected during the antibacterial therapy. She was treated with sulfamethoxazole and trimethoprim based on the susceptibility results, and a prophylactic dose was administered.

Chest and abdominal CT scans conducted on the third day of hospitalization did not show any abscess or inflammatory changes in the artificial blood vessel, and no deep abscess was detected. There were improvements, as indicated by a serum osmotic pressure of 291 mOsm/kg, serum sodium level of 143 mEq/L, and blood glucose level of 105 mg/dL on day 7 of hospitalization. Blood

Table 2. Endocrinological examination

Critical sample		Atrial blood gas			
Plasma glucose	38 mg/dL	pH	7.377		
HbA1c (NGSP)	5.8 %	pCO ₂	38.4 mmHg		
3-hydroxyacetic acid	1232 μmol/L	HCO ₃ ⁻	78.5 mEq/L		
Acetoacetic acid	688 μmol/L	BE	-2.8 mEq/L		
Total ketone body	1920 μmol/L	Na	141 mEq/L		
FFA	1980 μEq/L	K	4.37 mEq/L		
Insulin	3.4 μU/mL	Cl	111 mEq/L		
C-peptide	0.85 ng/mL	AG	12.4 mmol/L		
ACTH	214 pg/mL	Lac	0.8 mmol/L		
Plasma cortisol	22.7 μg/dL	Glucose	36 mmol/L		
IGF1	22 ng/mL				
GH	2.4 ng/mL				
TSH	3.011 μIU/mL				
fT3	2.24 pg/mL				
fT4	0.66 ng/dL				
NH3	37 μg/dL				
Urine test					
Ketone body	(-)				

Glucagon tolerance test	0 min	15 min	30 min	60 min
Plasma glucose (mg/dL)	38	85	103	103

glucose monitoring using the Dexcom G4 Platinum CGM system (San Diego, CA) revealed repeated hypoglycemic episodes at night and before meals. We considered the possibility that the patient's hyperglycemia was caused by unnecessary diazoxide medication. A controlled fast test and glucagon load test were conducted on day 9 of hospitalization, and the patient was again diagnosed with hyperinsulinemic hypoglycemia (**Table 2**). Diazoxide was resumed on the same day at the same dose as that before hospitalization (5 mg/kg per d). She was discharged from the hospital on day 20 of hospitalization after we confirmed that she did not show hypoglycemia after consuming cornstarch, and all diuretics were discontinued. Her HbA1c and plasma blood glucose levels were within the normal range after discharge from the hospital, and she had no hyperglycemic episodes with diazoxide.

Discussion

HHS has a reported mortality rate of 10–20% in adults and a poor prognosis (1). It is rare among children, but most cases are associated with new-onset type 1 diabetes or uncontrolled type 2 diabetes mellitus. Recently, more cases have been reported with an increase in the frequency of type 2 diabetes (1–3). Reports have indicated that the risk factors for HHS include complications of pneumonia and urinary tract infections, cerebrovascular accidents, drugs, peritoneal dialysis, burns, and dehydration (1, 3).

HHS is also caused by severe hyperglycemia due to the administration of glucocorticoids, excessive diuretics, and atypical antipsychotics (1). In our patient, the blood glucose level did not reach > 600 mg/dL, as defined by the ISPAD Clinical Practice Consensus Guidelines 2018 (2). Although there was no metabolic acidosis or ketosis, hyperglycemia and hyperosmolarity were observed. Based on these clinical findings, HHS was diagnosed. The development of new-onset diabetes mellitus in our patient was eliminated based on various antibody titers, HbA1c levels, and blood C-reactive protein levels at the time of hospitalization. Diazoxide-related adverse effects were initially suspected.

Several case reports have reported that HHS develops during the administration of diazoxide for hyperinsulinemia or insulinoma (3–6). A report indicated that the risk of diabetes or hyperglycemia increases when the blood diazoxide level is > 100 μg/dL (7). However, in our patient, the diazoxide level was only 25 μg/dL. Diazoxide is a renally excreted drug with a T_{1/2} of 15 ± 5.3 h, and steady-state serum concentrations are known to correlate with the dose of diazoxide (dose/kg per d).

Pharmacokinetic simulations have shown that there is no significant difference in steady-state serum concentrations between twice daily and three times daily divided doses, as long as the total daily dose is equivalent.

Previous reports have shown that once-daily administration or a higher daily dose of diazoxide than the recommended dose can result in higher serum

concentrations. The initial dose of diazoxide for pediatric patients (< 1 yr of age) with hyperinsulinemia is 5–10 mg/kg per d divided into three times a day up to a maximum of 15 mg/kg per d (7, 8). In this case, the patients were continuously taking diazoxide (5 mg/kg per d, twice a day); thus, we considered her serum concentration to be stable. In fact, the serum concentration of diazoxide after oral administration for 6 h was not high.

We believe that the pathophysiology of HHS in this case is not absolute insulin deficiency due to diabetes mellitus, but infection, diuresis, and relative insulin deficiency.

First, urinary tract infection causes overproduction of counterregulatory hormones, which leads to impaired glucose utilization and accelerated glycogenesis. This was followed by osmotic diuresis and dehydration. Next, the increase in hypotonic urine by furosemide worsened dehydration and hyperosmolality. In addition, a previous animal study showed that furosemide may worsen glucose intolerance and cause HHS (9). Finally, diazoxide suppressed insulin secretion, resulting in impaired glucose utilization.

The CHI guidelines recommend thiazide diuretics over loop diuretics; however, as noted above, diuretics can exacerbate hyperglycemia and hyperosmolality. Diuretics should be used cautiously in patients with CHI taking diazoxide (10).

Conclusion

In conclusion, regular blood glucose monitoring should be performed, and patients should be carefully monitored for hypoglycemia and hyperglycemia during diazoxide treatment. In addition, furosemide administration must be carefully considered during diazoxide treatment.

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