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Case Report

Oral Antidiabetic Drug Intoxication in a Toddler; Prophylactic Treatment or Follow Up?

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Abstract

Metformin is an oral anti-diabetic drug,which is used in type 2 diabetes mellitus therapy in adolescents and adults. Main side effects are headache, muscle pain, and gastrointestinal symptoms. Lactic acidosis is a rarely seen fatal side effect in therapeutic or excess doses. Hypoglycemia due to metformin treatment in adult population is indicated to be low but there is limited data in childhood since its usage is limited below 10 years of age. In this paper, consequences and therapeutic approach to high dose metformin intoxication in a 2 year old child is discussed

Keywords: Children; Metformin intoxication

Introduction

Metformin from biguanides group is an oral anti-diabetic drug, which is used in type 2 diabetes mellitus therapy in adolescents and adults. Its direct effect is increasing insulin sensitivity in peripheral tissues. It inhibits hepatic gluconeogenesis and increases the substrates (lactate, pyruvate). Inhibition of hepatic gluconeogenesis is the reason of fatal blood lactate increment with metabolic acidosis in therapeutic doses or excess dose [1,2]. Incidence of lactic acidosis in therapeutic doses has been identified as 3/100000 patient-year. Hypoglycemia is another side effect seen in therapeutic doses or excess dose. It is indicated to be low in the literature, but in a study in adult age group showed that the incidence is in-between 0% and 21% [3]. Due to the fact that metformin usage is limited in children, there isn't any research in this age group about metformin and its hypoglycemic effect. In this paper, we tried to discuss the consequences and follow up of high dose metformin intoxication in a 2 years old child.

Case

2 years old male child was admitted to Emergency Department (ED) with the history of two metformin 1000 mg tablet (125 mg/kg) intake which belongs to his grandmother 1 hour prior to admission. His mother found him chewing the tablets. His vitals were stable and physical examination was normal. There was not any pill esophagitis. Somatic maturation was appropriate for his age (weight:16 kg, 75-90 percentile; height:92 cm, 90-97 percentile; BMI:19kg/m^2, 95 percentile; bone age: 2 years). Complete blood count and biochemistry was normal besides mild AST elevation (46 U/L; normal range: 10-35 U/L).Gastric lavage was done and active charcoal was given in ED. 1500 cc/m^2 intravenous (iv) fluid as a maintenance treatment (glucose infusion rate 2,6 mg/kg/min) was started. Although oral feeding every 2-3 hour was maintained, patient's blood glucose levels were in between 70-80 mg/dl. A blood glucose level above 70 mg/dl was targeted and glucose infusion rate was increased gradually during follow up (Figure 1). Maximum glucose infusion rate was reached at 16th hour of drug intake (7,1 mg/kg/min). During his follow up;patient's blood sugar level increased above 100 mg/dl so glucose infusion rate was decreased and stopped 44 hoursafter drug intake. Although there was no acidosis in the blood gas (ph:7,49 pCO2:21,7 HCO3:16,2 BE:-5,3),patient's blood lactate levels were 2,78 mmol/L (normal range:1,3±0,6 mmol/L) in the blood gas and 22,1 mg/dl (normal range:10-14 mg/dl) in the serum so blood gas and serum lactate levels were followed (Table 1). 48 hours after drug intake, lactate level reached the highest value (3,04 mmol/L; 24,4 mg/dl).In the subsequent period, lactate level progressively decreased and achieved to normal range at the 120th hour of drug intake.

Patient's blood gases and renal function tests were within normal limits during follow up. Symptomatic hypoglycemia wasn't observed. Patient's AST level which was slightly higher than normal limits, decreased to the normal range on the 3rd day of hospitalization. The patient was discharged 7 days after hospitalization and was given an appointment to the pediatric endocrinology outpatient clinic one week later.

Discussion

Due to the increased usage of metformin in the treatment of type 2 diabetes, intoxication cases are seen more often. Although there are a large number of adult metformin intoxication cases, clinical data is limited in pediatric cases because of the limited usage of metformin below 10 years of age[4]. In a study of 41 cases, ages between 15 months and 17 years, who were reported to American Control Center

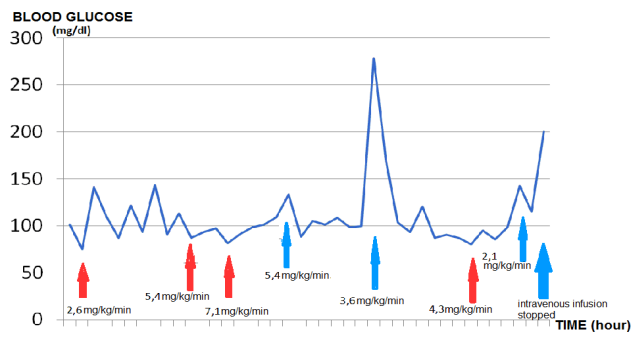

Figure 1: Graph showing blood glucose levels and glucose infusion rate of the patient.

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Table 1: Blood gas lactate and plasma lactate levels.

	Lactate level in the bloodgas (1,3±0,6 mmol/L)	Lactate level in the plasma (10-14 mg/dl)
Admission	2.78	22,1
24. hour	2,77	23,4
48. hour	3,04	24,4
72.hour	1,66	-
96. hour	2,05	-
120. hour	1,78	12,3

as metformin intoxication cases, it was reported that metformin intake dosage was in between 9-196 mg/kg in the cases below 6 years of age. The most common side effects were nausea, vomiting, diarrhea and dizziness [5]. In 38 patients blood glucose levels were checked and found within the normal range, in 22 patients blood gas results were evaluated and acidosis was not seen and in 2 patients blood lactate levels were evaluated and found within normal range. According to these results, it was concluded that metformin intoxication below 1700 mg was not problematic in healthy children. In our case patient was a 2-year-old toddler who has ingested 2000 mg metformin and according to this study he was in the high-risk group[6].

A 15 years old patient who took 38.25 g (0.55 g/kg) metformin, metabolic acidosis, increased blood lactate levels and abnormal kidney functions tests were observed, survival was obtained via multiple Hemodialysis and NaHCO3 treatment. Although NaHCO3 treatment is controversial, it was reported that NaHCO3 can be used in the treatment of patients who developed severe acidosis. It must be used carefully because it may shift oxyhemoglobine dissociation curve to the left, elevate the sodium load, change the Ca and K distribution and can cause reflex vasodilatation [4]. In our case, despite there was no acidosis in the blood gas, blood lactate level elevated and reached the highest value 48th hour after drug intake. It's known that 90% of the metformin is excreted from kidneys after oral intake and plasma half time of metformin was reported to be 6.2 hours. The blood halflife was reported to be 17.6 hours. We thought that although renal function tests were normal, the highest blood lactate levels reached 48 hour after drug ingestion because metformin is bound to the red blood cells longer than it is bound to plasma [7,8].

In the literature, there isn't a clear relationship between serum lactate level, serum metformin level and mortality [9]. However, in a study that analyzed metformin intoxication cases which had metabolic acidosis and elevated blood lactate levels, mortality risk was reported to be 83% in the cases whose blood ph<6,9 and serum lactate levels >25 mmol/L[10].In our case maximum lactate level was 3.04 mmol/L.

It is known that development of Central Nervous System (CNS) continues until 3 years of age and there are researches on the adverse effects of experienced neuroglycopenia to the development of CNS. It has been shown that hypoglycemia experienced during newborn period, causes neuronal damage to grey and white matter, cerebralcortex, hippocampus, basal ganglia, thalamus, brainstem and spinal cord [11]. Besides, severe degeneration atastrocytes and oligodendrocytes in the central nervous system were observed. These children, especially those experienced symptomatic hypoglycemia were observed to have more severe neurodevelopmental defects compared to asymptomatic patients. Increased risk of permanent brain damage and neurologic sequel has been reported in the cases, which experienced recurrent hypoglycemia[12]. In our case, there was no symptomatic hypoglycemia at the administration but patient was 2 years old and CNS development wasn't completed yet therefore he was more sensitive to effects of hypoglycemia. Also, hypoglycemic symptoms could not be determined clearly and severe hypoglycemia may be asymptomatic in this age group. Therefore we aimed a slightly hyperglycemic state during the follow up.

Increased use of biguanide group anti-diabetics brought out the risk of intoxication in childhood. Metformin intoxication must be kept in mind in the cases with increased blood lactate level and metabolic acidosis. There may be isolated lactate elevation without acidosis in blood gas and accompanying comorbidities may change the disease course, so the treatment plan should be made carefully considering patients age. We thought that,considering the possible negative neurocognitive effects of symptomatic and asymptomatic hypoglycemia in toddlers; in addition to frequent oral feeding, IV glucose support treatment may reduce the neurocognitive complications of high dose metformin intake.

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