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Metformin intoxication in an adolescent

To the Editor,

Metformin which belongs to the biguanide group is being used from the 1950's in diabetic patients who develop insulin resistance. Metformin is an anti-hyperglycemic agent and provides euglycemia. The known toxic effect of biguanides is lactic acidosis in acute and chronic use. Fenformin which belongs to the biguanides was recalled from market in USA in 1976. Lactic acidosis related to acute excessive metformin may be fatal (1). Here, a patient who was followed up with metformin intoxication has been presented.

A 15-year-old female patient was referred to our emergency department because of metformin intoxication. Gastric irrigation was performed and activated charcoal was administered in the patient who had abdominal pain following ingestion of 40 tablets containing 1000 mg metformin with the objective of suicide. At the same time, intravenous dextrose was given as bolus, since the blood glucose was found to be 28 mg/dL. On physical examination in the emergency department, the consciousness was confused, marked agitations were found occasionally and Kussmaul respiration became prominent. The patient was internalized in the intensive care unit. At the time of presentation the blood glucose was found to be 112 mg/dL, but decreased to 35 mg/dL because of possible venous access problem. Intravenous dextrose was given rapidly and 10% dextrose fluid therapy was continued. Blood gases revealed the following: pH 6.99, HCO₃ 6.3 mmol/L, PCO₂ 27.3 mmHg, BE -22.7 mmol/L, lactate level 134 mg/dL (0.4-2.2). Laboratory findings were as follows: Hb 12.5 g/dL, WBC 17000 mm³, platelets 389000 mm³, urea 21 mg/dL, creatinine 1.97 mg/dL, sodium 123 mEq/L, potassium 3.1 mEq/L. Blood gases measured six hours after complementary bicarbonate treatment was started were as follows: pH 6.95, HCO₃ 5.4 mmol/L, PCO₂ 26.1 mmHg, BE-27.3 mmol/L. The patient whose respiratory distress increased was intubated at the 8th hour of hospitalization. Central venous dialysis catheter was inserted in the right jugular

vein. Dopamin treatment was started because of development of hypotension and continuous veno-venous hemodiafiltration was performed as 120 ml/min. The first hemodiafiltration procedure was performed using dialysis fluid for 10 hours. The patient was extubated 8 hours after intubation. On the second day of hospitalization lactate was found to be 93.3 mg/dL, urea was found to be 64 mg/dL and creatinine was found to be 1.4. Veno-venous hemodiafiltration was performed again using 120 ml/min blood and dialysis fluid for 24 hours. On the 4th day of hospitalization, laboratory findings were as follows: pH 7.44, HCO₃ 22 mmol/L, PCO₂ 45.3 mmHg, BE -1.5 mmol/L, lactate 7 mg/dL, urea 20 mg/dL, creatinine 0.53, sodium 135 mEq/l, potassium 3.7 mEq/l. The patient was discharged from the intensive care unit and on the 10th day of hospitalization was discharged from the hospital.

The effect of causing lactic acidosis in chronic use of metformin has been found in 1-10/100 000 patients. The mortality rate was found to be 45% in a series of 49 patients who developed lactic acidosis after metformin treatment (2). In this study, the variables which predicted mortality were reported to be liver failure and prolonged prothrombin time. In our patient, there was no liver failure and prolongation of prothrombin time. Metformin-related lactic acidosis is mostly related with acute overdose of metformin. Blood gases and lactate values were shown to be the two possible variables which predicted mortality in a study. In this study which evaluated 22 patients, 16 patients who had a pH level above 6.9 and a lactate level below 225 mg/dL survived, while 5 of 6 patients who had a pH level below 6.9 and a lactate level above 225 mg/dL died (3). In our patient, blood pH level decreased to 6.95 and lactate level increased to 230 mg/dL. However, lactate levels and blood gases became normal as a result of early and efficient hemodiafiltration intervention. Hypoglycemic side effect of metformin may occur when used in combination with other oral antidiabetics. In addition, hypoglycemia may develop in metformin overdose. Therefore, attention should be paid to hypoglycemia in patients

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who present with metformin overdose. In our patient, marked hypoglycemia was observed for two times and the necessary intervention was performed. Bicarbonate treatment is controversial in metformin-related lactic acidosis. Administration of bicarbonate may cause recurrent metabolic alkalosis, serum potassium and calcium disorders and myocardial dysfunction. Hemodialysis was shown to be efficient in treatment of metformin-related lactic acidosis. In patients with severe metabolic acidosis, intensive bicarbonate treatment has been reported to be inefficient and hemodialysis has been recommended, if $\text{pH} < 7.1$ in patients with renal problems (4). In addition, continuous veno-venous hemodiafiltration has also been shown to be effective. However, hemodiafiltration has been reported to have a lower effect on the excretion of the drug compared to traditional hemodialysis (5). It should be performed in patients who can not tolerate hemodialysis and who have instable hemodynamics. In our patient, intensive bicarbonate treatment was not useful and hemodiafiltration was performed at the 10th hour of hospitalization. In the literature, four patients (two from our country) who developed lactic acidosis related to metformin intoxication have been reported (6,7,8,9). In female gender and patients aged 14-16 years, lactic acidosis developed after ingestion of excessive doses of metformin (25-63 g). One patient survived after bicarbonate treatment, one patient survived after hemodialysis and 2 patients survived after continuous veno-venous hemodiafiltration.

In recent years, cases of obesity and hence type 2 diabetes have increased. Increased use of metformin dictates that pediatricians and pediatric endocrinologists obtain more information about the side effects of this drug. We would like to emphasize that bicarbonate treatment is not efficient and early

hemodialysis or hemodiafiltration are life-saving in patients who develop severe acidosis ($\text{pH} < 7.1$).

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References

1. Lalau JD, Mourlhon C, Bergeret A, Lacroix C. Consequences of metformin intoxication. *Diabetes Care* 1998; 21: 2036-7.
2. Lalau JD, Race JM. Lactic acidosis in metformin-treated patients. Prognostic value of arterial lactate levels and plasma metformin concentrations. *Drug Saf* 1999; 20: 377-84.
3. Dell'Aglio DM, Perino LJ, Kazzi Z, Abramson J, Schwartz MD, Morgan BW. Acute metformin overdose: examining serum pH, lactate level, and metformin concentrations in survivors versus nonsurvivors: a systematic review of the literature. *Ann Emerg Med* 2009; 54: 818-823.
4. Lalau JD, Andrejak M, Morinière P et al. Hemodialysis in the treatment of lactic acidosis in diabetics treated by metformin: a study of metformin elimination. *Int J Clin Pharmacol Ther Toxicol* 1989; 27: 285-288.
5. Harvey B, Hickman C, Hinson G, Ralph T, Mayer A. Severe lactic acidosis complicating metformin overdose successfully treated with high-volume venovenous hemofiltration and aggressive alkalinization. *Pediatr Crit Care Med* 2005; 6: 598-601.
6. Lacher M, Hermanns-Clausen M, Haefner K, Brandis M, Pohl M. Severe metformin intoxication with lactic acidosis in an adolescent. *Eur J Pediatr* 2005; 164: 362-365.
7. Harvey B, Hickman C, Hinson G, Ralph T, Mayer A. Severe lactic acidosis complicating metformin overdose successfully treated with high-volume venovenous hemofiltration and aggressive alkalinization. *Pediatr Crit Care Med* 2005; 6: 598-601.
8. Doğru O, Koken R, Bukulmez A, Yurumez Y, Ovalı F. Metformin overdose: a case report. *Journal of the Indian Society of Toxicology* 2005; 1: 41-45.
9. Gura M, Devrim S, Sagiroglu AE, Orhon Z, Sen B. Severe metformin intoxication with lactic acidosis in an adolescent: a case report. *The Internet Journal of Anesthesiology* 2010; 27: 2.