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Case Report

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Clinical management of metformin overdose: A case report

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ABSTRACT

Metformin is first-line therapy in diabetes mellitus treatment. Metformin intoxication may cause lactic acidosis. A 29-year-old woman presented to our emergency department with loss of consciousness. Arterial blood gas revealed severely increased anion gap lactic acidosis. Continuous venovenous hemofiltration was performed for 39 h. After extracorporeal treatment, the acidosis resolved and the patient became conscious. There is no specific treatment for metformin intoxication; current treatment is supportive only. Our aim is to highlight the diagnosis, chromatographic measurement of the drug blood level, and management of metformin overdose.

1. Introduction

Metformin is in the biguanide drug class and is less likely to cause lactic acidosis than phenformin. Therapeutic doses of metformin do not cause hypoglycemia and patient compliance is better with this drug (Misbin,1977; Luft et al.,1983). The incidence of metformin-associated lactic acidosis (MALA) is 5-9 cases per 100,000 patients (Stang et al., 1999; Von Mach et al., 2004). Lactic acidosis is described as a blood la ctate level greater than 5 mmol/L and a blood pH below 7.35 (Misbin,1977). MALA has a mortality up to 50% and has been reported in the settings of chronic use and acute overdose (Luft et al., 1983; Stang et al., 1999; Von Mach et al., 2004). Here, we report an acute metformin toxicity associated with hypoglycemia and wide anion gap metabolic acidosis.

2. Case Report

A 29-year-old woman presented to our emergency department with loss of consciousness. She had no history of intoxication or medical illness. On arrival, the patient's Glasgow Coma Scale score was 4 (E1M2V1). The vital signs were: blood pressure 70/50 mmHg, pulse rate 60 beats per minute, and respiratory rate 20 breaths per minute. Capillary blood glucose level was 24 mg/dL. It was learned that the patient had no oral feeding problem. Her liver function tests were within normal limits. Initial arterial blood gas testing revealed a pH of 6.90. The anion gap was 20.9 mmol/L and lactate was 16.55 mmol/L (Table 1). Arterial blood gas testing showed severely increased anion gap lactic acidosis. Intravenous (IV) dextrose was started to correct hypoglycemia. Additionally, IV sodium bicarbonate was administered.

Drug particles were seen during gastric lavage; therefore, activated charcoal was administrated. Toxicology tests including opioids, barbiturates, benzodiazepines, ethyl alcohol, acetaminophen, salicylates, and tricyclic antidepressants were negative. Metformin was analyzed by high-performance liquid chromatography (Fig. 1). Severe metabolic acidosis was treated with IV 30 mEq/h sodium bicarbonate; hypoglycemia was treated with IV 10% dextrose. Because of refractory hypotension, IV 10 µg.kg−1.min−1 dopamine and 10 µg.kg−1.min−1 norepinephrine were administered. After 2 h, hemodialysis was started. In the seventh hour, hemodialysis was stopped because of worsening hemodynamic instability and increasing lactic acidosis level (Table 1). Continuous venovenous hemofiltration (CVVHDF) was started after confirmation of metformin overdose; the serum metformin level was 169.35 µg/mL (Figure 1). CVVHDF was performed for 39 h. After CVVHDF treatment, pH was 7.38 and lactate was 2.25 mmol/L (Table 1). The patient's Glasgow Coma Scale score improved to 15 (E4V5M6) after 12 h of CVVHDF. The patient said she had attempted suicide by ingesting 70 metformin tablets (70 g). She was discharged on the ninth day of admission.

Table 1. Acid base disorders on admission, after hemodialysis and CVVHD

	Admission	Hemodialysis	CVVHDF	Reference values
pH	6.9	7.06	7.38	(7.35-7.45)
pCO2 (mmHg)	38.2	12.4	22.9	(35-45)
pO2 (mmHg)	99	136	71	(75-100)
Anion Gap	31	32.6	7	(8-16)
HCO3 (mmol/L)	8	3.4	13.4	(21-25)
Na (mEq/L)	139.9	140	135.4	(132-152)
K (mEq/L)	3.8	3.5	3.6	(3.3-4.8)
Cl (mEq/L)	111	115	115	93-110
Lactate (mg/dL)	16.55	20.6	2.25	0.9-1.7
Glucose (mg/dL)	5	110	112	(74-110)
BUN (mg/dL)	12	7	7	(10-50)
Creatinine(mg/dL)	1.62	0.7	0.8	(0.5-1.4)

Chromatographic Method

A 10 mL blood sample was collected from subject; the sample was centrifuged at 2500 rpm for 10 min. The serum obtained was separated and frozen at -20 °C until the time of analysis. To a 0.5 mL aliquot of serum sample 0.5 mL acetonitrile were added to precipitate protein and the mixture was vortexed for one minute, than centrifuged at 3500 rpm for 10 min. The liquid phase was transferred to another tube and then the sample was diluted 1:20 by volume with acetonitrile. The injection volume into the HPLC-DAD system ranged from 5-40 µL. Chromatographic experiments were performed using an Agilent 1100 series system (Agilent Technologies, Waldbronn, Germany), which included a G1311A gradient delivery pump, a G1329B robotic autosampler, a G1315A diode-array detector, a G1322A vacuum degasser and a G1316A thermostatted column compartment. A Kromasil 100-5C18 analytical column (4.6 × 150 mm, 5 µm particle size, Hichrom, UK), protected by a guard column filled with the same material, was used. The HPLC analysis was performed using an adaptation of the method with some modifications of Moore et al. A standard calibration curve consisted of five concentration points of 12.5, 25, 50, 75 and 100 ng of metformin (Moore et al., 2003). Each concentration point was performed for three times. Working Standard solution (2.5 ng/mL), was prepared on the day of assay. The calibration curve was constructed using a series of metformin dilutions. As expected, a very high metformin concentration (169.35 µg/mL) was measured in the serum sample (Figure 1).

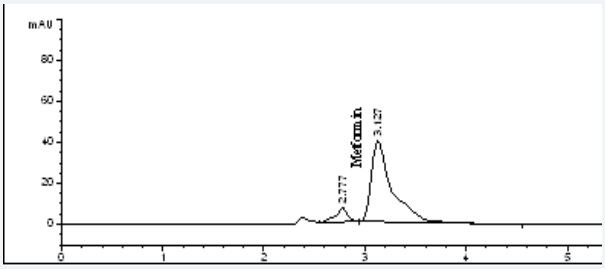

Fig. 1.

3. Discussion

Wide anion gap metabolic acidosis in a drug overdose should alert clinicians to metformin intoxication (Perrone et al., 2011). MALA can present with anorexia, lethargy, nausea, vomiting, epigastric pain, hypotension, hypothermia, respiratory failure, and cardiac dysrhythmia (Gan et al., 1992; Spiller, 1998; Von Mach et al., 2004). Our patient presented with profound hypoglycemia. Hypoglycemia may occur in the setting of MALA (Cullen et al., 2004). Hemodialysis and CVVHDF are useful in acid–base disorders and to remove causes of lactic acidosis (Spiller, 1998). Sodium bicarbonate should be considered in patients with normal respiratory functions if their blood pH is lower than 7.0 (Yang et al., 2009). This approach has no significant effect on mortality and may cause detrimental effects, including decreased cardiac output, decreased intracellular pH, and paradoxical increased lactate production (Luft et al., 1978). Other complications may include volume overload, hypernatremia, and left shift of the oxyhemoglobin dissociation curve (Gan et al., 1992). A large cohort study of patients treated for MALA failed to show a significant benefit for bicarbonate infusion, and in our patient, sodium bicarbonate infusion did not increase blood pH despite her lactate level increasing to 24 mmol/L (Bruijstens et al., 2008) (Table 1). Hemodialysis with a bicarbonate buffer is successful in MALA treatment (Lalau et al., 1987; Soyoral et al., 2011).

In addition to drug removal, bicarbonate dialysis can rapidly correct acid–base disorders (Lalau et al., 1987; Spiller, 1998). Because of the drug's low molecular weight and lack of protein-binding, metformin has a high plasma clearance with conventional dialysis modalities (Lalau et al., 1987; Soyoral et al., 2011). Our patient could not tolerate hemodialysis for the required time. After 7 h of hemodialysis, she was hemodynamically unstable; therefore, CVVHDF was the treatment of choice in this case (Davenport et al., 1993). Wide distribution of metformin allows continuous hemodialysis or hemoperfusion to maximize metformin remo-

val (Yang et al., 2009). In this case, CVVHDF was performed for 39 h. After CVVDHF, the patient's pH improved to 7.38 and her lactate level decreased to 2.25 mmol/L. Early diagnosis and treatment of hypoglycemia and lactic acidosis may provide complete recovery in metformin intoxication. The treatment for metformin intoxication is usually supportive only. Vasopressors can be used if there is refractory hypotension. Accurate and prompt diagnosis is mandatory in metformin overdose. In hemodynamically unstable patients, hemodialysis with bicarbonate buffer may be inadequate, and CVVHDF should be considered for prompt metformin removal.

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Conflict Of Interest
The authors declare they have no conflict of interest.

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