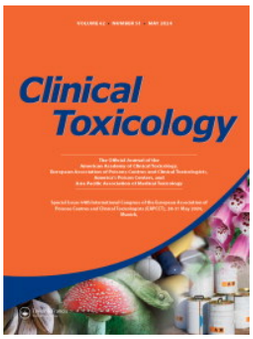

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Patrick Nisse, Monique Mathieu-Nolf, Marc Deveaux, Xavier Forceville & Alain Combes

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LETTER

A Fatal Case of Metformin Poisoning

To the Editor:

Metformin hydrochloride, a biguanide medicine, is used to improve glucose tolerance in patients with type II non-insulin dependent diabetes mellitus. This medication is considered safe if not used in the presence of contraindications like renal failure, liver disease, alcohol abuse, or congestive heart failure (1). Severe lactic acidosis, which carries a high potential mortality risk, has been reported in patients following overdoses (2,3). This letter is a reminder of the severe toxicity that can result from metformin overdose.

A 42-yr-old male was admitted to the hospital with confusion and abdominal pain. He had a 10-yr history of non-insulin dependent diabetes mellitus. One year ago, metformin was stopped and the patient was placed on insulin therapy. His current medications included insulin, clarithromycin, domperidone, ibuprofen, buflomedil (a peripheral vasodilator), and tiaprofenic acid (a non-steroidal anti-inflammatory drug). On the admission, the patient was conscious but confused. He mentioned attempting suicide the day before but could not specify the drug. His temperature was 35.5°C, pulse was 70 beats per minute (bpm), blood pressure 100/45 mmHg, respiratory rate 38 bpm. He was oliguric and appeared dehydrated. His initial arterial blood gas results were pH 6.88, pO_2 159 mmHg, pCO_2 13.8 mmHg, SaO_2 97%, and bicarbonate 2.9 mmol/L. The lactate concentration was 27 mmol/L. Other laboratory values were sodium 143 mmol/L, potassium 4.1 mmol/L, chloride 99 mmol/L, L, calcium 2.7 mmol/L, urea nitrogen 4.2 mmol/L, creatinine 163 μmol/L, and glucose 16.4 mmol/L. The blood count was hemoglobin 18.7 g/dL, hematocrit 57.2%, white blood cells 19,260/mm^3 (neutrophils 76%), and platelet count 336,000/mm^3. Toxicologic screening tests for methanol, ethylene glycol, ethanol, and acetaminophen were negative. Traces of ketones were detected in the urine. Chest and abdominal X-rays were normal, fiberoptic endoscopy of the upper gastrointestinal tract showed erythematous esophagitis and a congestive and ulcerous gastritis. Electrocardiogram was normal. He was treated with intravenous fluids [normal saline and hydroxyethyl starch (an esterified starch solution used for volume expansion), insulin, trace elements, and minerals. After a few hours, the patient was intubated and ventilated because of decreasing level of consciousness. Ventilation was conducted with high minute ventilation for acidosis. Bradycardia was treated with epinephrine. A blood sample was obtained just before continuous veno-venous hemodyalisis. Despite hemodyalisis, the severe lactic acidosis persisted: arterial pH 6.87, pO_2 65.27 mmHg, pCO_2 48.61 mmHg, SaO_2 86% ($FiO_2 = 100\%$, $PEEP = 8$), and lactate 15.2 mmol/L. The blood urea nitrogen was 3.9 mmol/L and creatinine 124 μmol/L. Fifteen hours after admission, he developed acute respiratory distress syndrome, anuria and shock requiring a dopamine drip (5 then 20 μg/kg/min) followed by an epinephrine drip (up to 25 mg/hour just before the death). Under epinephrine 3 mg/h, hemodynamic monitoring revealed a low cardiac index of 2.4 L/min/m^2 and a low pulmonary wedge pressure at 5 mmHg, despite volume expansion (3 L of normal saline and 2 L of hydroxyethyl starch). The patient died from a shock refractory 34 h after admission. Metformin was identified and quantified by a reference laboratory (4) as a plasma concentration of 188 μg/mL.

In this case, ingested drug was unknown on admission. The diagnosis of metformin intoxication was suspected on the clinical data and confirmed by measuring metformin in plasma. Death was probably due to a severe lactic acidosis secondary to the metformin overdosage. Metformin-induced lactic acidosis is associated with a number of risk factors. Renal impairment may have been related to dehydration and non-steroidal anti-inflammatory medications (ibuprofen and tiaprofenic acid) administration (5). Acute renal failure increases metformin levels, which are correlated with serum creatinine concentrations in renal insufficiency (6).

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A high metformin plasma concentration decreases glucose utilization and increases lactate production by hepatocytes. Because of the high metformin concentration (188 μg/mL), it is likely that this patient has ingested a very large amount of metformin. The therapeutic plasma metformin concentration is 0.5–2.5 μg/mL. Levels above 5 μg/mL are generally seen in metformin-associated lactic acidosis (7). Neither arterial lactate levels nor plasma metformin levels have been of prognostic significance in relation to mortality (8). Prognosis depends more on factors other than metformin concentrations, specifically underlying conditions that increase lactate production, reduce lactate elimination, or impair circulatory function (9). Hemodialysis initiated late in the course of a metformin overdose has not been demonstrated to be helpful.

Patrick Nisse
Monique Mathieu-Nolf
Centre Antipoison
Centre Hospitalier Régional Universitaire
Lille, France

Marc Deveaux
Institut de Médecine Légale
Faculté de Médecine
Université de Lille
Lille, France

Xavier Forceville
Alain Combes
Réanimation Polyvalente
Centre Hospitalier
Meaux, France

REFERENCES

1. Pearlman BL, Fenves AZ, Emmett M. Metformin-associated lactic acidosis. Am J Med 1996; 101(1):109–110.
2. Stang MR, Wysowski DK, Buttler-Jones D. Incidence of lactic acidosis in metformin users. Diabetes Care 1999; 22(6):925–927.
3. Barrueto F, Meggs WJ, Barchman MJ. Clearance of metformin by hemofiltration in overdose. J Toxicol Clin Toxicol 2003; 40(2):177–180.
4. Deveaux M, Dallet P, Quintin C, Nisse P, Gosset D. Ultra-short determination of metformin in plasma by hydrophilic interaction liquid chromatography. Ann Toxicol Anal 2002; XIV(2):125–128.
5. Chan NN, Fauvel NJ, Feher MD. Non-steroidal anti-inflammatory drugs and metformin: a cause for concern? Lancet 1998; 352:201.
6. Lalau JD, Lacroix C, Compagnon P, de Cagny B, Rigaud JP, Bleichner G, Chauveau P, Dulbecco P, Guerin C, Haegy JM. Role of metformin accumulation in metformin-associated lactis acidosis. Diabetes Care 1995; 18(6):779–784.
7. Kruse JA. Metformin-associated lactic acidosis. J Emerg Med 2001; 20(3):267–272.
8. Lalau JD, Race JM. Lactic acidosis in metformin-treated patients. Prognostic value of arterial lactate levels and plasma metformin concentrations. Drug Saf 1999; 20(4):377–384.
9. Lalau JD, Mourlhan C, Bereget A, Lacroix C. Consequences of metformin intoxication. Diabetes Care 1998; 21:2036–2037.

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