

CASE REPORTS

ated with movement, dislodgment, or malfunction of the biomedical device.⁴⁻⁶

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Anesthesiology

1997; 87:1003-5

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Lippincott-Raven Publishers

Lactic Acidosis as a Serious Perioperative Complication of Antidiabetic Biguanide Medication with Metformin

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BIGUANIDES have been established in the therapy of non-insulin-dependent diabetes mellitus for decades. However, after the introduction of sulfonylureas, biguanides were nearly eliminated from the market, largely because of the risk of severe lactic acidosis.¹⁻⁴ In the United States, use of biguanides was stopped in 1976 for this reason.³ In 1995, the biguanide metformin was approved for the US market.^{2,5} The advantage is that biguanides reduce hyperglycemia with only a very low risk for hypoglycemia.^{2,6} In addition, they have a positive effect on blood lipid concentration and lead to a mild weight reduction in obese patients.^{5,7} Again, how-

ever, the most important risk is the development of severe lactic acidosis.^{1,4}

Little information is available in the current anesthesia literature about the perioperative management of patients who receive biguanides. The following report describes the clinical course of a patient receiving metformin therapy who developed severe lactic acidosis after minor surgery.

Case Report

A 66-yr-old man was admitted for surgical repair of an abdominal wall hernia. He had a history of hypertension, non-insulin-dependent diabetes mellitus, peripheral vascular disease, obesity, and a previous pulmonary embolism. On admission, the patient was in good health. His arterial blood pressure, blood glucose, creatinine, and blood urea nitrogen levels were within normal limits. His medications were nifedipine, isosorbide mononitrate, metformin, and phenprocoumon (coumarin). After the coumarin was replaced by intravenous heparin, the patient had an uncomplicated hernia repair, which was performed with the patient during fentanyl/N₂O/isoflurane balanced anesthesia. His immediate postoperative course was uncomplicated, and he was discharged from the postanesthesia care unit to a surgical ward. The patient's regular medications, including a single dose of metformin (500 mg/day), were administered on the day before surgery but were not given on the day of surgery. From postoperative day 1 on, the regular medication was administered again. During his

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Received from Klinik für Anästhesiologie und Operative Intensivmedizin der Christian-Albrechts-Universität, Kiel, Germany. Submitted for publication August 22, 1996. Accepted for publication June 11, 1997.

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Key words: Biguanides. Complications. Diabetes mellitus. Lactic acidosis. Metformin. Postoperative anesthesia.

4 days on the ward, the patient was hypertensive (150/90–180/90 mmHg) and had a heart rate in the upper normal range (80–100 beats/min). The patient received 2,500–3,500 ml fluid per day, partly intravenously and partly as enteral nutrition. Although the caloric input was low (400–800 kcal/day) the blood glucose concentration showed hyperglycemic values between 200 and 280 mg/dl. Urine excretion and creatinine clearance were not documented, but serum creatinine and blood urea nitrogen, measured on the first and second postoperative day, were within normal range (creatinine, 1 mg/dl; blood urea nitrogen, 13 mg/dl). On the second postoperative day, the patient reported dyspnea for the first time. He was treated with oxygen and theophylline, and his abdominal bandage was loosened. Despite initial improvement, he had to be transferred to the surgical intensive care unit on postoperative day 4 for increasing respiratory distress and hypotension. On admission there he was somnolent and had a fever (39.7°C). During the next 2 h, his condition worsened dramatically, necessitating intubation and hemodynamic support with catecholamines. The patient showed the symptoms of systemic inflammatory response with an acute decrease of the leukocytes count and platelets, body temperature greater than 40°C, metabolic acidosis (pH 7.32; base excess –12.5), and a serum lactate concentration of 95 mg/dl. His renal function worsened rapidly and he became oliguric. Within 12 h the serum creatinine level increased from 2.5 mg/dl to 3.3 mg/dl and the blood urea nitrogen level increased from 31 mg/dl to 46 mg/dl. An intraabdominal abscess, central line induced sepsis, urosepsis, mesenteric infarction, endocarditis, and pulmonary embolism were ruled out. The only pathologic finding was a small hyperdense pulmonary area, seen in the thoracic computed tomography scan and interpreted as a localized pneumonia. Therefore, the combination of metformin, hypocaloric alimentation, and respiratory infection was deemed the most probable cause for his severe lactic acidosis.

Symptomatic therapy was started, and metformin was discontinued. The patient was mechanically ventilated with a fractional concentration of oxygen in inspired gas of 0.7 to 1.0 adjusted to arterial blood gas analysis. Volume resuscitation and catecholamine support were optimized by pulmonary artery catheter monitoring. In the first 24 h after admission to the intensive care unit, the patient received 8,500 ml volume, including hydroxyethyl starch 6%, human albumin 5%, packed erythrocytes, and fresh frozen plasma. This permitted a reduction in infused catecholamine doses. The cardiac index remained between 2.5 and 3.0 $l \cdot m^{-2} \cdot min^{-1}$. The heart rate decreased from 130 beats/min to 95 beats/min, and the arterial blood pressure increased from 60/40 mmHg to 110/50 mmHg. The metabolic acidosis (lowest pH , 7.185) was buffered with a total amount of 1,080 mmol $NaHCO_3$ 8.4% until a pH within the normal range was achieved. Hyperglycemia was treated with intravenous insulin. For renal support and as an attempt to eliminate metformin, venovenous hemofiltration was performed. Hemodialysis, the standard therapy for metformin-induced lactic acidosis, was not deemed appropriate during this unstable hemodynamic situation.

The patient's condition improved considerably during the next 4 days. Catecholamine support and hemofiltration were discontinued. The patient regained consciousness and was weaned from the respirator. However, 2 days later (10 days after surgery), the patient's status deteriorated again. Multiple-organ failure developed, beginning with pulmonary insufficiency followed by renal and cardiac failure. After 7 weeks of intensive therapy, the patient died. The autopsy showed a purulent pneumonia of both lungs. Findings in the heart, liver,

kidneys, and intestines were consistent with prolonged circulatory shock. No other cause for the initial metabolic acidosis was found.

Discussion

Biguanides are used for therapy of non-insulin-dependent diabetes mellitus. They inhibit gluconeogenesis in the liver and kidney, increase the non-insulin-dependent uptake of glucose in skeletal muscles, and reduce the concomitant hypertriglyceridemia and hypercholesterolemia.^{6,8} Biguanides act by fixation to mitochondrial membranes, leading to lower intracellular adenosine triphosphate and higher adenosine monophosphate concentrations. Glucose is metabolized anaerobically.³ The resulting pyruvate is reduced to lactate, which is usually metabolized quickly in the liver. The patient might show a moderate lactatemia but no lactic acidosis.⁶ If this mechanism fails, severe lactic acidosis will develop, followed by multiple-organ dysfunction, a complication associated with a poor prognosis.^{1,4} Metformin is the only available biguanide in the United States. It is superior to phenformin, another biguanide, available in Europe, because the incidence of lactic acidosis is 20 times lower.⁷ Nevertheless, lactic acidosis still occurs. Therefore, it is essential that the anesthesiologist is aware of the contraindications for biguanides, especially renal insufficiency,^{1,4,6} because metformin is eliminated by the kidneys.^{1,5,6} Some authors recommend regular measurement of creatinine clearance in patients receiving biguanide therapy.¹ Further contraindications are cardiac, pulmonary, and hepatic insufficiency; hypoxia; severe infections; alcohol abuse; and pregnancy.^{3–6}

With the exception of hemodialysis, the therapy recommended for biguanide-induced lactic acidosis is symptomatic.³ The underlying pathologic changes (*i.e.*, the blockade of the mitochondrial respiratory chain) cannot be treated. Our patient had severe lactic acidosis after minor surgery. No contraindications for metformin except a low postoperative caloric input could be found. Some authors recommend that metformin be stopped 2 days before surgery.⁹ Based on our limited experience with perioperative metformin management, we changed our departmental policy after this case and now stop metformin therapy several days before and after surgery. If the metformin cannot be omitted before operation, as in emergency cases, we suggest that patients should be monitored for serum lactate concentration, arterial blood gas analysis, and renal performance perioperatively.

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Conclusions

Due to the metabolic advantages over sulfonylureas, metformin has become popular for treating non-insulin-dependent diabetes mellitus. Nevertheless, it is important to be aware of the possible severe side effects of this therapy, especially induction of lactic acidosis.

The authors thank their colleague Rainer Kohrs, M.D. (Charlottesville, VA), for his critical reading of the English version of this manuscript.

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