Postoperative Lactic Acidosis in Patients Receiving Metformin

To the Editor.—We appreciate the case report by Merck et al. (Anesthesiology 1997; 87:1003–5) regarding postoperative lactic acidosis in a patient receiving metformin. Although we praise the authors for wisely stopping the metformin after diagnosing the patient's systemic inflammatory response syndrome, we disagree with their conclusion that metformin contributed to the acidosis and with their decision to routinely stop metformin administration for several days perioperatively.

As the authors noted, the association of biguanides (metformin, phenformin, and buformin) with metabolic acidosis led to their removal from the United States in 1977. An initial review contained 430 cases of lactic acidosis in diabetic patients taking biguanides; however, only 12 cases involved patients taking metformin, and each of the 12 patients had significant renal insufficiency (the lowest creatinine was 3.0 mg/dl). Renal insufficiency is now a contraindication for metformin because it is excreted by the kidneys. Accumulation of metformin, as in a patient with renal insufficiency who continues to receive the drug, can result in elevated lactate levels and death.

It is unlikely that Merck et al.'s patient had an elevated metformin level after receiving only 500 mg/day for postoperative days 1–4, with normal renal function on postoperative days 1 and 2. Given that the half-life of metformin in patients with normal renal function is only 1.7–1.5 h and that doses up to 2,550 mg/day result in therapeutic metformin levels, this patient's total dose of 2,000 mg during 4 days would not cause elevated levels. The authors considered hemodialysis and used venousousus insufation to eliminate metformin in their patient, but we believe that these treatments were not indicated without elevated metformin levels.

Metformin has never been proven to be detrimental in patients without contraindications. This is not surprising: at therapeutic levels, metformin does not significantly inhibit oxidative phosphorylation, as does phenformin; therefore, metformin causes, at most, a minimal increase in lactate. Metformin was used in Canadians without contraindications for 56,000 patient-years without any reported cases of lactic acidosis. Also, in a study of diabetic patients presenting to the emergency room, the incidence of lactic acidosis was not higher in patients taking metformin than those given sulfonylureas or insulin.

The effects of therapeutic levels of metformin are unknown during type A lactic acidosis (e.g., hyperperfusion from sepsis). The high mortality of patients with type A acidosis probably is caused by the degree of hyperperfusion, as reflected by the lactate ion level, not the result of the hyperlactatemia itself. Lalau et al. reported metformin-associated lactic acidosis in 14 patients; the 4 patients without elevated metformin levels had worse prognoses because their lactic acidoses were purely caused by hyperperfusion compared with patients who had lactic acidoses partly because of metformin accumulation. Similarly, a study of 20 patients with metformin-associated lactic acidosis showed that most patients with elevated metformin levels did well, whereas those with therapeutic or low levels had a high mortality. Therefore, even if the therapeutic metformin level contributed to a worsening lactic acidosis, it is doubtful that this would adversely affect morbidity.

In conclusion, we believe that the risks of continuing metformin perioperatively are minimal. There are potential benefits to continuing the drug; patients are more likely to arrive for surgery with better diabetic control, which could result in improved wound healing, decreased infection rates, and decreased need for perioperative insulin. For patients scheduled for major surgery (with the possibility of hypoperfusion), we recommend eliminating only the day of surgery dose because this should result in a minimal metformin level at the time of surgery. Even if a patient were to suffer a serious insult, their metformin level would be low. If concern develops that a perioperative event may have resulted in renal compromise, metformin should not be restarted until renal function is determined to be normal. For ambulatory surgery (with negligible risk of hypoperfusion), we continue administration of metformin on the day of surgery and recommend that patients take it as usual after discharge.

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Specific Therapies of Biguanide-induced Lactic Acidosis

To the Editor:—Mercker et al.1 reported a case of severe biguanide-induced lactic acidosis. However, the authors did not discuss specific therapies. In such case, the administration of sodium dichloracetate (DCA) should have been considered. DCA is an antidiabetic agent that activates the pyruvate dehydrogenase complex, the mitochondrial enzyme that catalyzes the conversion of pyruvate to acetyl-coenzyme A and carbon dioxide. In dogs DCA has been reported to correct lactic acidosis induced by phenformin, another biguanide that induces lactic acidosis more commonly.2 In the patient described, an ongoing infection could have contributed to the overproduction of lactate. Even in endotoxin-induced lactic acidosis, DCA administration has been shown to reduce blood lactate levels.3 Administration of DCA could reduce plasma lactate levels in patients with lactic acidosis caused by various etiologies, even though in a large clinical trial, such intervention did not improve survival rates.2

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References


In Reply.—We appreciate the interest and comments of our colleagues regarding our case report and would like to thank the editorial board for the opportunity to respond.

We agree with Lustik et al. that a patient’s diabetes mellitus should be under good control perioperatively. Therefore we would not stop metformin administration without starting an alternative therapy if appropriate.

Nevertheless, we are much more concerned about perioperative metformin medication than Lustik et al. are. The patient mentioned in our case report was treated according to the recommendations suggested by Lustik et al. He presented no contraindications for metformin (except low caloric input) until he developed severe lactic acidosis. Therefore stopping metformin could prevent a rare, but significant, risk for the patient, whereas the potential benefits of continuing the drug are rather vague.

According to the new manufacturer’s recommendations in Germany, metformin should be omitted 2 days before and after general anesthesia. The risk to develop perioperative problems that would...