Phenformin-induced Lactic Acidosis and Anesthesia

John A. Reitan, M.D.,* Roger B. Stephens, M.D., † Marion A. Warbinski, M.D.†

Phenformin (N-β-phenethylbiguanide), an oral hypoglycemic agent, has been associated with lactic acidosis in several reports. This case concerns an adult diabetic patient seen in the emergency room because of a surgical abdomen and severe acidosis.

REPORT OF A CASE

A 43-year-old Caucasian man, known to be diabetic, taking phenformin (DBI), 200 mg daily, entered the Sacramento Medical Center emergency room at 12:00 noon with a three-hour history of malaise and pain in the left lower quadrant. He was ambulatory, but in obvious pain and respiratory distress. The respiratory rate was 40-50/min, blood pressure 300/170 torr, pulse 140/min in sinus rhythm, and rectal temperature 99.5 F. Laboratory values were: hemoglobin 17.5 g/100 ml; sodium 130 Eq/l, potassium 3.5 mEq/l; blood glucose 150 mg/100 ml; trace ketonuria; creatinine 8.0 mg/100 ml; lactate 175 mg/100 ml; lactate/pyruvate ratio 42. Duplicate temperature-corrected arterial blood-gas values were: pH 6.80, P CO2 10 torr, P O2 75 torr. In view of the severe acidosis, abdominal pain with rigidity, and absent bowel sounds, a diagnosis of acute mesenteric vascular occlusion was entertained and the patient was sent to the intensive care unit for acid-base and cardiovascular stabilization prior to operation. Heart failure was suspected because of moist rales in all lung fields, a CVP of 23-27 cm H2O, and a portable chest roentgenogram showing "possibly early pulmonary edema." The patient was given furosemide, 120 mg, in divided doses, and, in addition, he received NaHCO3, 659 mEq, over the next three hours to treat the base deficit of more than 35 mEq/l. A repeat arterial blood pH was then 7.24. During this time the blood pressure decreased to 70/40 torr, and intermittent lactic acidosis was noted. Prior to operation he became alert, the blood pressure increased, and the vasopressor was stopped.

Upon arrival in the operating room, laboratory values included a pH of 7.26, Na+ 150 mEq/l, and K+ 6 mEq/l. The blood pressure was 110/60 torr, pulse 90/min and regular, respiratory rate 28/min, and CVP 14 cm H2O. Anesthesia was induced with sodium thiopental, 100 mg, in divided doses, and NaO 50 per cent- O2 50 per cent, followed by slow intravenous administration of d-tubocurarine, 24 mg. The trachea was intubated with ease, and vital signs remained stable for approximately 10 minutes. As laparotomy began, the patient showed signs of inadequate anesthesia, and Innovar, 1 ml (2.5 mg droperidol and 0.05 mg fentanyl), was infused intravenously. Blood pressure became unobtainable, and pulse increased to 110/min, the ECG showing a junctional rhythm. Ephedrine sulfate, 50 mg, iv, did not re-establish the blood pressure. A slow infusion of norepinephrine increased the blood pressure to 110/50 torr, and the pulse reverted to a normal sinus rhythm at 100 beats/min. The patient was given additional NaHCO3, 178 mEq, over 15 minutes, and an arterial blood-gas sample thereafter showed pH 7.26, P CO2 28 torr, and P O2 74 torr. The CVP increased to 18 cm H2O, and when another dose of NaHCO3 was started, pulmonary rales developed and the blood pressure decreased to 70/30 torr. Infusion of isoproterenol for 10 minutes restored the pressure and relieved the rales. The patient received 1,600 ml of 5 per cent dextrose in water during the operation. The esophageal temperature remained 98-99 F. No cause for the acidosis was found at operation, and at the end the vital signs were stable at a blood pressure of 110/60 torr, pulse 95 beats/min in sinus rhythm, and CVP 14 cm H2O. Throughout the procedure there was no ECG evidence of hyperkalemia. The patient was taken to the ICU responsive and complaining of incisional pain. Over the next 18 hours he received additional NaHCO3, 401 mEq, and arterial pH returned to within normal limits (7.41). Serum potassium level decreased to 4.2 mEq/l. Postoperative blood glucose levels ranged from 100 to 450 mg/100 ml and the patient was treated intermittently with regular insulin. At no time during his hospitalization did the patient have significant urinary ketones or marked glycosuria. During his recovery he developed a mild metabolic alkalosis from continued nasogastric suction, which was treated by increased fluid administration and diuretics (acetazolamide). Mild transient right hemiparesis and homonymous hemianopsia were noted postoperatively. The patient was discharged on the tenth postoperative day, still complaining of slight pain in the left lower quadrant.

DISCUSSION

The mechanism by which phenformin produces relative hypoglycemia is unknown; tentatively, it is thought to inhibit mitochondrial oxidative metabolism and facilitate anaerobic pathways, with a subsequent increase in lactic
acid production. This metabolic alteration is thought to be the cause of the acidosis associated with phenformin therapy.

The intact drug and its metabolites are excreted by the kidney, and accumulation of the drug occurs with reduced renal clearance. Consequently, impaired renal function has been present in most reported cases of phenformin acidosis. On admission our patient's creatinine clearance was 9 ml/min and his serum creatinine at least four times normal. However, clearance improved to 88 ml/min (low normal), and creatinine was 1.9 mg/100 ml before his discharge. In view of the above values, the reduced renal function and lactic acidosis were probably subacute, that is, slowly developing over a few days, and this patient must be considered a diabetic with diminished renal function.

The cause of the patient's initial marked hypertension is enigmatic. In general, most patients with severe metabolic acidosis are hypo- or normotensive. The low blood pressures in other reported studies could be due to pre-existing shock (as a cause for lactic acidosis) or to the loss of vessel and cardiac tone from significant electrolyte shifts caused by the acidosis. As a speculation in our case, an extraordinary renin–angiotensin cycle may have been instigated, with the resultant blood pressure of 300/170 torr.

The balance between augmenting left heart failure and correction of the acidosis by sodium bicarbonate was delicate. This dilemma was illustrated by the development of rales and an increasing CVP when the fifth intraoperative ampule of bicarbonate was started. Chemically-induced positive inotropy by isoproterenol reversed the problem. In retrospect, the administration of Tris buffer (THAM) was indicated for alkalinization in this case, since it potentially neutralizes intracellular acidosis faster without the hazard of a high sodium load. Interestingly, the first calculated base excess in our patient was approximately minus 35 mEq/l. His weight was 84 kg, and assuming a 45 per cent bicarbonate distribution space, he had a deficit of 1323 mEq of bicarbonate (84 × 0.45 × 35). During hospitalization he received 1,260 mEq of sodium bicarbonate before the acid–base balance approached normal.

The morbidity and mortality from phenformin-induced lactic acidosis have been high. A recent report of vigorous alkalinizing therapy for nine patients resulted in the extraordinary recovery rate of 78 per cent. Maintenance of proper cardiovascular function is essential for survival from the acidosis. Cardiac output and central as well as peripheral responses to catecholamines diminish during severe acidosis. For example, our patient responded poorly to ephedrine sulfate intraoperatively. The use of norepinephrine as a pressor agent may augment the metabolic acidosis by reducing peripheral perfusion, and isoproterenol is the cardioactive drug of choice. Moreover, anesthetic drugs with alpha-blocking (vaso-dilating) potential, such as droperidol, should be avoided. Our patient tolerated anesthesia well until a small amount of Innovar was infused and profound hypoten-sion ensued.

The action of digitalis glycoside is variable in severe acidosis. Its poor inotropic response is probably the result of intracellular potassium and calcium shifts. We chose not to use digitalis for the heart failure because of its possible toxic effects. The patient's renal clearance was diminished, which could have led to retention of the drug. Furthermore, the potential for a rapidly decreasing extracellular/intracellular K⁺ ratio from the vigorous alkalinization and the resultant opportunity for ventricular dysrhythmia were present. Finally, the questionable augmentation of myocardial contractility by digitalis in severe acidosis led us to use isoproterenol as a positive inotropic agent instead.

In spite of early aggressive therapy, our patient suffered mild temporary CNS damage, probably during one of the intraoperative hypotensive episodes. An added physiologic insult undoubtedly occurred with operation, yet abdominal pain is a common early symptom in phenformin lactic acidosis and, with nausea and vomiting, may be the presenting complaint.

A continuing increase in the number of reported cases of phenformin-induced lactic acidosis has shown the entity to be far more widespread than previously envisioned. Anesthesiologists in the operating room and
intensive care units should be aware of this startling syndrome and the need for immediate, energetic therapy.

REFERENCES


Metabolism

FFA AND MYOCARDIAL METABOLISM The arterial and coronary sinus concentrations as well as myocardial extraction of free fatty acids (FFA), glucose, lactate, and pyruvate were measured at rest in healthy, fasting male subjects. The arterial FFA concentrations demonstrated a significant negative linear correlation with myocardial extraction of glucose, lactate, and pyruvate, but were independent of the arterial concentrations of glucose and lactate. When the arterial FFA concentrations rose above 800 μmol/l, a significant efflux of pyruvate into the coronary sinus was observed.

These results suggest that FFA can depress glucose uptake in the human heart, due in part to the inhibition of pyruvate dehydrogenase. In addition, the relationship between arterial FFA concentration and myocardial lactate extraction indicates that FFA concentrations should be taken into consideration when calculating the per cent extraction of lactate by the human heart as an indicator of myocardial ischemia.

Further studies were carried out in two groups of subjects after 2 hours of supine leg exercise. One group, which received a continuous infusion of nicotinic acid during the period of exercise, showed a much lower arterial FFA concentration, but unaltered concentrations of glucose, lactate, and pyruvate. The suppression of the exercise-induced rise in arterial FFA concentration was associated with increased myocardial extraction of glucose, lactate, and pyruvate, suggesting again that in man a reciprocal relationship exists between arterial FFA concentrations and myocardial metabolism of carbohydrate substrates. (Carlson, L. A., and others: The Relationship in Man Between Plasma Free Fatty Acids and Myocardial Metabolism of Carbohydrate Substrates. Cardiology 57: 51-54, 1972.)