Metformin and Lactic Acidosis

Guilt by association?

Probably the most common mechanism by which metformin elevates blood lactate is by inducing catecholamine release in those who regulate or prescribe it. Caution in restricting the use of metformin for the treatment of type 2 diabetes has been rationalized on the basis of *1*) its chemical identity as a biguanide, 2) its ability to modify hepatic intermediary metabolism, 3) its administration to individuals who may already be at heightened risk for developing lactic acidosis, and *4*) limited epidemiological data comparing the incidence of lactic acidosis in patients with diabetes who were treated with metformin compared with those who were not. Given our current understanding of the clinical pharmacology of metformin and the results of the important population-based study by Brown et al. (1) in this issue, it is fitting to reexamine the association between metformin and lactic acidosis relative to the caveats listed above.

Metformin carries the toxicological baggage of its biguanide predecessor, phenformin, which was withdrawn from the U.S. market ~20 years ago because of an estimated incidence of up to 1 case of phenformin-associated lactic acidosis per 1,000 patient-years. Most cases were in patients with preexisting renal or hepatic failure or myocardial disease (2,3), all of which independently predispose to lactic acidosis (4). Why phenformin may, while metformin may not, increase the chance of developing lactic acidosis may largely be due to differences in their interaction with the liver.

The liver is quantitatively the most important site of both glucose production and lactate clearance. During fasting, pyruvate and, hence, lactate are shunted toward gluconeogenesis, in part by an increase in the activity of the mitochondrial enzyme pyruvate carboxylase. In the fed state, oxidation of pyruvate to acetyl coenzyme A is the principal route of hepatic lactate removal, and the rate of this reaction is governed by the activity of the mitochondrial pyruvate dehydrogenase enzyme complex (4).

Phenformin inhibits the hepatic uptake and oxidation of lactate and increases the extrahepatic splanchnic production of lactate (5). At least some of these actions may be due to the binding of phenformin to the mitochondrial membrane, which impairs the transport of reducing equivalents, such as NADH. This effect, in turn, inhibits the two major pathways of lactate disposal: gluconeogenesis and oxidation. Thus, the glucose-lowering and lactate-raising properties of phenformin are inexorably linked, by virtue of the drug's effects on mitochondrial function.

The critical question is whether the adverse effects of phenformin on lactate homeostasis represent a "class effect" common to other biguanides. This is probably not the case. Although metformin inhibits hepatic glucose output (6), I am not aware of convincing data that demonstrate this effect is mediated by disrupting mitochondrial membrane function or is associated with inhibition of mitochondrial oxidative metabolism. Moreover, metformin is excreted unchanged in the urine, whereas phenformin undergoes partial biotransformation by the liver to an inactive metabolite. Liver disease per se would therefore be expected to predispose to phenformin-associated lactic acidosis, by reducing the rate of phenformin catabolism. In contrast, liver disease would be expected to have relatively little effect on the kinetics and metabolism of metformin.

Renal insufficiency can raise circulating concentrations of both biguanides. In the case of phenformin, higher drug levels may further inhibit lactate removal by both liver and kidney, so the well-established association between phenformin administration and hyperlactatemia in diabetic patients who have renal insufficiency is understandable. In contrast, blood levels of metformin do not appear to correlate with lactic acidosis (7), as might be predicted for a drug that does not significantly impair the oxidative catabolism of lactate.

As Brown et al. (1) summarize, previous epidemological investigations conducted here and abroad failed to demonstrate a significantly increased association between lactic acidosis and metformin administration. Their own study confirms and extends these findings by examining the rate of lactic acidosis in three ethnically and geographically diverse populations of U.S. citizens with type 2 diabetes who were never exposed to metformin or, presumably, to any other biguanide. In over 41,000 person-years of experience, Brown et al. (1) found only four unequivocal and three possible cases of lactic acidosis—a trivial incidence. Not surprisingly, these authors found that each definitive or possible instance of lactic acidosis coexisted with one or more serious conditions that could have precipitated or exacerbated the acidosis. This observation is consistent with that of a large, prospective investigation of the natural history and course of acquired lactic acidosis in adults (8). That study showed that by the time lactic acidosis was diagnosed, nearly all patients had both hemodynamic (e.g., hypotension) and metabolic (e.g., liver or renal disease) underlying causes of impaired lactate metabolism.

As Brown et al. (1) acknowledge, their study may have underestimated the true rate of lactic acidosis in patients not exposed to metformin, because of underreporting in medical records, because hyperlactatemia was not sought by the patients' physicians, or because patients were preselected to receive the drug only if they were at low risk for complications. On the other hand, the data may also be marginally inflated. For example, a diagnosis of "possible" lactic acidosis included cases in which an increased anion gap was calculated. However, the anion gap is a relatively insensitive indicator of abnormal lactate metabolism, even in patients with hyperlactatemia (4,9). In addition, the blood lactate concentration may be artificially elevated if the specimen is not obtained, processed, and analyzed under conditions that minimize ex vivo glycolysis by leukocytes and erythrocytes. These conditions may not often be met in a nonresearch environment.

A logical next step in evaluating metformin's toxicity would be to prospectively determine the rate of lactic acidosis in patients similar to those described by Brown et al. (1) but who were receiving

metformin. Because the incidence of lactic acidosis in premetformin subjects appears to be quite low, it might be assumed that a modest increase in rate would be easy to detect and to ascribe to metformin treatment. However, given the complex etiology of lactic acidosis in critically ill patients, the inherent limitations of population-based studies of this type, and the current safety profile of metformin, I suspect it will be devilishly hard to identify with certainty anything less than a major adverse effect of the drug on acid-base metabolism.

Is it time to revise the package insert on metformin?

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