Lactic Acidosis in Metformin Therapy

Relationship between plasma metformin concentration and renal function

Metformin belongs to a class of drugs known as the biguanides that are widely used in the treatment of NIDDM. Its association with lactic acidosis is well established, although rare (1).

Metformin undergoes rapid renal excretion (2–5). After oral administration of metformin, ~90% of the absorbed dose is rapidly excreted unchanged in the 12-h urine. Drug clearance is four to five times that of creatinine. According to these pharmacokinetic aspects, it is firmly established that occurrence of lactic acidosis linked to metformin necessitates, overdose excepted, metformin accumulation by renal failure (1). Indeed, close correlations between plasma metformin and creatinine clearance have been found in subjects with normal renal function, as well as in patients with moderate or severe renal failure (4,6).

We report the case of a metformin-treated patient with lactic acidosis and metformin accumulation that was an exception to the rule in that massive metformin accumulation contrasted with a mild increase in serum creatinine. A 65-year-old man with NIDDM of 10 years' duration treated with metformin 850 mg b.i.d. was admitted with a 1-day history of abdominal pain predominant on the left side, vomiting, liquid stools, and tachypnoea. His medical history also revealed hypertension treated with diuretics (thiazide plus spironolactone), hepatitis B, and constipation. Physical examination revealed a distended abdomen with diminished bowel sounds. Vital signs included a rectal temperature of 36.3°C, a pulse rate of 110 beats/min, and a systolic blood pressure of 130 mmHg. Urine output was 0–20 ml/h. An abdominal X-ray showed a typical intestinal obstruction pattern. The peripheral arterial blood gas analysis performed on admission demonstrated lactic acidosis: pH 7.13, bicarbonate 5 mmol/l, and lactate 24.5 mmol/l. Dipstick urinalysis was positive for ketone bodies. Other laboratory findings included (serum): glucose 15 mmol/l, blood urea nitrogen 6 mmol/l, creatinine 129 μmol/l, potassium 6 mmol/l, hematocrit 0.55, and proteins 80 g/l. The creatinine clearance, calculated from Cockcroft's formula (7), was 67 ml/min. Hepatic function tests (glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, γ-glutamyl-transpeptidase, and alkaline phosphatase) were normal. Plasma metformin concentration (measured using high-performance liquid chromatography) was dramatically high at 61 mg/l, compared with a normal overnight value of 0.6 ± 0.5 mg/l (SD) in diabetic subjects chronically taking 850 mg of metformin b.i.d. or t.i.d. (6).

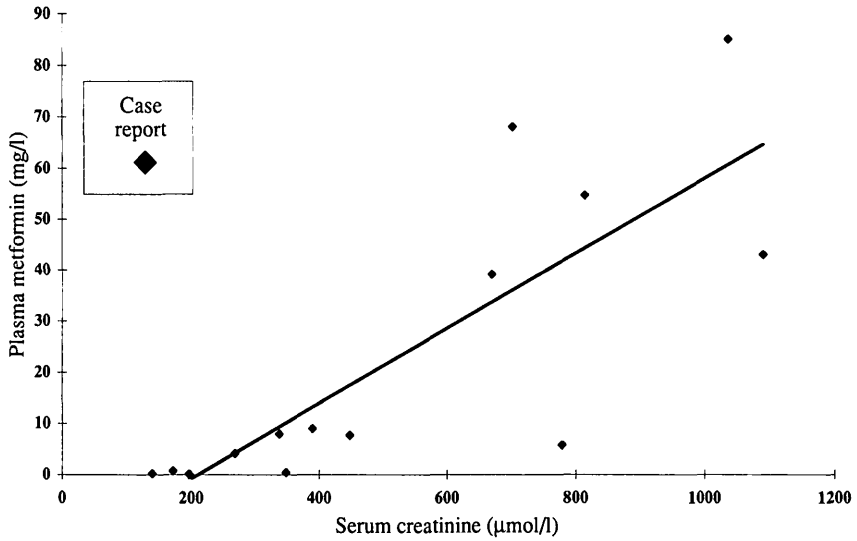

Figure 1—*Relationship between plasma metformin concentration and serum creatinine in the case report and in a previous study of metformin-treated patients with lactic acidosis (n = 14, r = 0.81, P < 0.001). Adapted from Lalau et al. (6).*

An exploratory laparotomy was rapidly performed after intubation, mechanical ventilation, and intravenous administration of dextrose, insulin, dopamine, dobutamine, and 170 mmol of sodium bicarbonate. The laparotomy revealed a volvulus of the sigmoid colon linked to a megacolon. Sigmoid resection and colostomy were performed. After surgery, arterial blood parameters improved: pH 7.30, bicarbonate 10 mmol/l, and lactate 17 mmol/l. Patient recovery was then rapidly complete. Mechanical ventilation was stopped on day 3, and the patient was discharged from the intensive care unit with regular insulin on day 8.

Plasma metformin and serum creatinine concentrations in this case report were compared with published data. There is only one study of metformin-treated patients with lactic acidosis and available plasma metformin concentrations (6). In this study, serum creatinine was in close correlation with plasma metformin (coefficient of correlation $r = 0.84$, $P < 0.001$), and those patients with the highest values (39.1–84.9 mg/l) were anuric (serum creatinine 670–1,091 μmol/l). Compared with that study, the patient in this case report had among the highest values of metformin, while the serum creatinine concentration was the lowest one.

The present observation raises questions concerning the pathophysiology of hyperlactatemia and metformin accumulation and the aggravation of the latter during the first hours of hospitalization. With regard to hyperlactatemia, because of the intestinal damage and because the mild increase in serum creatinine would discount a priori a major metformin accumulation, intestinal occlusion could be a reasonable explanation. However, in intestinal catastrophes lactate does not reach the level noted here: in a study of 30 patients with intestinal occlusion and lactic acidosis (J.D.L., unpublished observations), we have noted a much lower mean lactate value (8.3 ± 3.1 mmol/l). Consequently, the hyperlactatemia might be related to the metformin accumulation, which was finally evidenced.

With regard to metformin accumulation, the plasma metformin concentration was among the highest values ever observed, while serum creatinine was not markedly increased. How can such a discrepancy be explained? The first assumption is that of a time lag between the occurrence of the oligoanuria and the increase in serum creatinine. A second mechanism may be postulated in relation to the underlying

pathology, namely, the intestinal occlusion and the intestinal handling of metformin (8). Under physiological conditions, intestinal concentrations of metformin are indeed 10–100 times those of plasma (9). There is, however, no clear evidence that metformin is retained along the intestinal wall within the cellular compartment. A third mechanism whereby metformin may accumulate would consist of an interaction between organic cation transport systems of the renal proximal tubule that normally eliminate biguanides and an unknown substance possibly related to the intestinal occlusion. Such a hypothesis is supported by the observation that cimetidine, a guanidine analogue (10), inhibits the renal tubule secretion of metformin (11).

The continuing increase in plasma metformin concentration during the first hours of hospitalization remains to be interpreted. This increase may reflect the relative worsening of the renal function and/or the effect of the last drug intake.

It is noteworthy that neither a lactate level of 24.5 mmol/l nor a metformin level of 100 times the mean therapeutic level had prognostic value with regard to patient outcome.

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Four Years After the Diabetes Control and Complications Trial Report: Nonimplementation in High-Risk Patients

The Diabetes Control and Complications Trial (DCCT) (1) demonstrated that the incidence of diabetic retinopathy, nephropathy, and neuropathy can be reduced by intensive, as opposed to conventional, treatment of hyperglycemia. We initiated a study to determine whether the conclusions of the DCCT were being implemented in patients with existing severe microvascular complications of diabetes.

We identified all patients of Hudson Valley Eye Surgeons who had undergone panretinal argon laser photocoagulation for treatment of diabetic retinopathy over the 3-year period from July 1994 to July 1997. Laser treatment had been initiated for proliferative diabetic retinopathy in accordance with the Diabetic Retinopathy Study (2). We contacted these patients and asked a series of questions related to the management of their diabetes. These questions were designed to determine their method of glycemic control, the number of injections of insulin they were administering, their frequency of glucometer self-testing, and their incidence of hypoglycemic reactions. We also asked patients whether they were familiar with glycosylated hemoglobin, whether and when they had been tested, and what their most recent level had been. Finally, they were asked whether they were familiar with the DCCT and if they stated that they were, what the conclusions of that study were. In addition, we contacted the physician with primary responsibility for management of glycemic control in these patients and asked for the date and result of the most recent glycosylated hemoglobin.

We identified 104 patients who had undergone argon laser panretinal photocoagulation for proliferative diabetic retinopathy within the previous 3 years. Of these, seven patients had died since completing treatment, three could not be contacted, and one refused to participate. We excluded two patients currently undergoing hemodialysis for diabetic nephropathy. The remaining 91 patients were questioned. Of these 91 patients, 23 had type 1 diabetes, with an average duration of 28.5 years. Mean age of the type 1 diabetic patients was 44 years (median 44.5, range 25–69). There were 17 female and 6 male type 1 diabetic patients. The remaining 68 patients had type 2 diabetes. Their mean age was 67 years (median 67, range 46–84), and there were 42 females and 26 males in this group. Their average known duration of diabetes was 19 years.

All patients with type 1 diabetes were on insulin injections. Of the type 2 diabetic patients, 43 were being treated with insulin, 20 were on oral hypoglycemic agents, and 5 were being treated by dietary means alone.

Only 1 of the 23 type 1 diabetic patients and 2 of the 68 type 2 diabetic patients used three or more injections per day. In the group with type 1 diabetes, 9 used one daily injection, 2 used one or two daily, 10 used two injections daily, and 1 used two or three injections each day. Of the patients with type 2 diabetes, 13 were on one insulin injection daily, 4 used one or two a day, 22 used two injections daily, and 4 used two or three injections daily.

All 23 patients with type 1 diabetes self-tested glucose levels using a glucometer. Of the 68 type 2 patients, 33 self-tested blood glucose levels. None of the