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Lactic Acidosis in Metformin Therapy

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Abstract

The biguanide drugs metformin and phenformin have been linked in the past to lactic acidosis, a metabolic condition associated with high rates of mortality. Although concern over the hyperlactataemic effect of phenformin led to the withdrawal of this drug from clinical practice in the 1970s, the situation with metformin has been less clear. Retrospective data indicate that, in metformin-treated patients with lactic acidosis, neither the degree of hyperlactataemia nor accumulation of metformin is of prognostic significance. Furthermore, the lowest rates of mortality were seen in patients with high plasma concentrations of metformin, which has led to the hypothesis that the drug may confer some benefit, linked to an increase in vasomotility, in such cases.

Overall, it appears that mortality in patients receiving metformin who develop lactic acidosis is linked to underlying disease rather than to metformin accumulation, and that metformin can no longer be considered a toxic drug in this respect. These findings are likely to be of considerable relevance to the management of patients with type 2 (non–insulin-dependent) diabetes mellitus, especially where such patients are elderly.

It has been recognised for many years that biguanide therapy may be related to lactic acidosis,[1,2] a condition associated with high mortality rates (30 to 50%).[3] Metformin has been linked with this metabolic disorder, but with an incidence 10 to 20 times lower than that seen with phenformin.[4,5] Because of this association with a high incidence of lactic acidosis, phenformin was withdrawn in 1977. Whether the difference between the 2 drugs is simply one of incidence or extends to the outcome of lactate and drug accumulation remains to be confirmed.

1. Prognostic Value of Arterial Lactate Levels and Plasma Metformin Concentrations

A possible difference in the nature of lactic acidosis was first postulated 12 years ago after the survival of 5 metformin-treated patients with lactic acidosis, 3 of whom had circulatory shock.[6] To determine whether plasma lactate and/or metformin levels are related to outcomes in these patients, 3 retrospective analyses were carried out. The first involved 624 patients with a mean age of 58 ± 18 years with hyperlactataemia (arterial lactate level >5 mmol/L), none of whom had been treated with metformin (data not published). In the second analysis, a series of 49 metformin-treated patients of mean age 68 ± 10 years with lactic acidosis (arterial lactate level >5 mmol/L; pH ≤7.35) was studied. The third analysis involved 13 patients of mean age 47 ± 16 years with reported metformin overdosage. In studies 2 and 3, arterial lactate and plasma metformin levels were compared with final outcomes.

It is interesting to note that 2 studies carried out in the 1970s[7,8] showed mortality rates of about

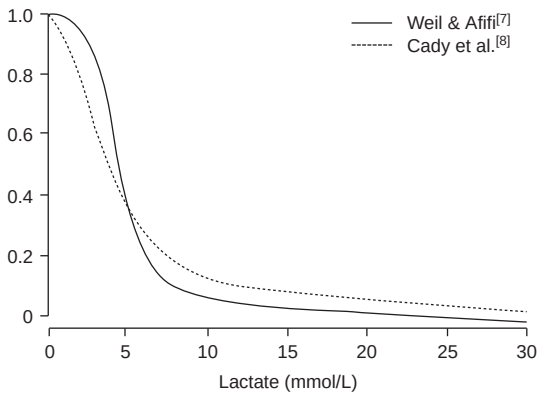

Fig. 1. Relationship between arterial lactate levels and outcome in 2 series of metformin-untreated patients from the 1970s.[7,8]

50% for lactate levels above 2.7 mmol/L in patients who were not treated with metformin (fig. 1). The more recent data from patients not treated with metformin (study 1) show a similar overall mortality rate (56%), although this was associated with much higher arterial lactate levels (median 7.2 mmol/L).

Median arterial lactate levels and plasma metformin concentrations in relation to survival or mortality in study 2 are presented in figure 2.[9] Plasma metformin concentrations of up to 1 mg/L are classified as normal, with drug accumulation being apparent at concentrations of 5 mg/L and above. In metformin-treated patients there was no clinically relevant difference in median lactate level between patients with lactic acidosis who survived (13.0 mmol/L) and those who died (14.3 mmol/L). The median plasma metformin level was 3 times higher in the surviving patients (20.6 *vs* 6.3 mg/L). Patients with the lowest plasma metformin concentrations (≤1 mg/L) appeared to have the poorest prognosis (only 1 of these 6 patients recovered), while patients with the highest plasma concentrations of metformin (≥5 mg/L) appeared to have the best prognosis (23 of these 35 patients recovered, with plasma metformin concentrations of up to 68 mg/L).

Figure 3 shows the distribution of lactate levels in survivors and patients who died. The proportion of patients who had an arterial lactate level of at least 10 mmol/L was higher in the group of patients who died (91 *vs* 62%). Proportions of patients who survived and those who died were similar in the range of arterial lactate levels of 15 to 29 mmol/L; above this range, the highest arterial lactate level (35.5 mmol/L) was seen in a patient who survived. This suggests that arterial lactate levels are of no prognostic significance, even where these levels are as high as 35.5 mmol/L.

The improved prognosis in patients with the highest plasma concentrations of metformin was not related to less severe hyperlactataemia, since median lactate levels were similar for patients with high and low plasma metformin concentrations. As hyperlactataemia has no prognostic value and high plasma concentrations of metformin are associated with an improved prognosis, it therefore appears likely that concurrent disease is the determinant of outcome for each patient. Indeed, each patient had at least one additional risk factor for lactic acidosis (e.g. major organ failure, haemorrhagia, sepsis), and two or more risk factors were present in 28

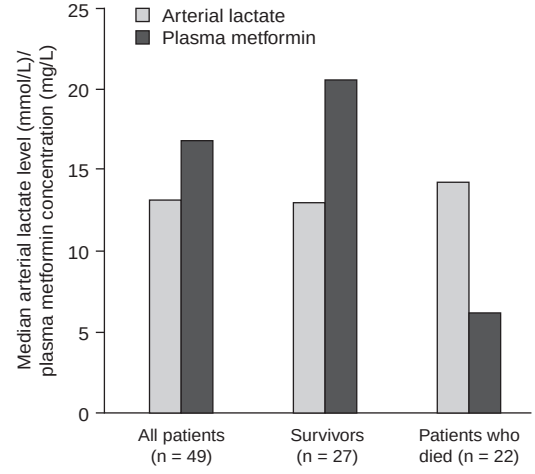

Fig. 2. Median arterial lactate levels and plasma metformin concentrations shown as a function of outcome in 49 metformin-treated patients with lactic acidosis (study 2).[9]

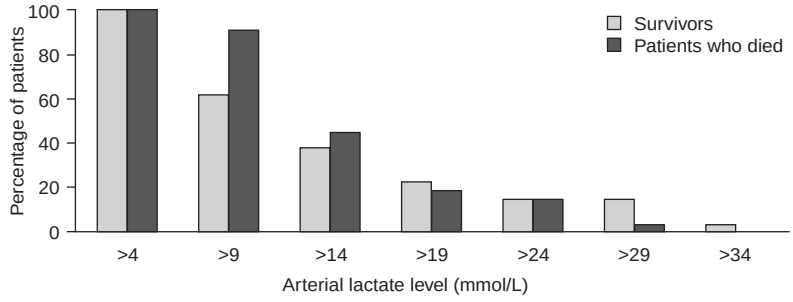

Fig. 3. Distribution of arterial lactate levels in metformin-treated patients who survived and those who died (study 2).[9]

patients (2 risk factors in 19 patients, 3 in 8 and 4 in 1) [table I].

On the basis of these findings, the premise that the prognosis of lactic acidosis in patients treated with metformin is determined by high plasma drug concentrations, with no account being taken of concurrent medical conditions (e.g. sepsis, haemorrhage) that predispose to or provoke hyperlactataemia, appears to be incorrect. This presumption has been perpetuated in the literature and has led to an erroneous perception of metformin as an inherently toxic agent. For example, data published in the *New England Journal of Medicine*[10] show characteristics for a series of 56 metformin-treated patients with lactic acidosis (table II) and compare a number of variables for patients who survived and those who died, but there is no mention of plasma metformin concentrations or coexisting disease.

The importance of plasma metformin concentration measurement is illustrated by the case of a 62-year-old patient treated with metformin who developed anuria and lactic acidosis.[11] Biochemistry showed the patient to have a serum creatinine level of 4 mg/dl, arterial lactate level of 16.3 mmol/L and arterial pH of 7.09. As metformin therapy was not stopped, a high plasma concentration of the drug might have been expected in this patient, with the conclusion that lactic acidosis was linked to metformin accumulation. In fact, the plasma concentration of metformin was 0.4 mg/L (well within the therapeutic range) because anuria in this patient was linked to sudden cardiovascular failure.

Four sources of error in the study of the relationship between metformin and lactic acidosis have therefore been identified:

- overestimation of the prognostic significance of hyperlactataemia in general
- overestimation of the prognostic significance of hyperlactataemia in patients treated with metformin
- failure to measure and report plasma metformin concentrations
- underestimation of the prognostic significance of associated hyperlactataemic disorders.

Moreover, although any link between metformin and lactic acidosis can obviously be eliminated in patients with low plasma concentrations of the drug, high plasma concentrations are still not synonymous with metabolic disorders. Analysis of patients with metformin overdosage (study 3)[12]

Table I. Medical conditions predisposing to or precipitating lactic acidosis in metformin-treated patients (study 2; n = 49). All patients had at least 1 condition/risk factor, 19 had 2, 8 had 3, and 1 patient had 4 concurrent conditions[9]

Condition	No. of patients
Renal failure	36
Cardiovascular failure	15
Sepsis	12
Haemorrhage	7
Hepatic failure	7
Pulmonary failure	7

Table II. Comparative characteristics (± standard deviation) of a series of metformin-treated patients with lactic acidosis[9]

	Patients who died	Patients who survived
Number	29	27
Mean age (y)	70.5 ± 2.7	67.3 ± 2.1
Mean arterial lactate level (mmol/L)	15.9 ± 1.9	11.2 ± 1.3
Mean metformin dosage (mg/day)	1260 ± 145	1350 ± 115
No. with serum creatinine level ≥1.5 mg/dl	16	7
No. with serum creatinine level <1.5 mg/dl	1	8

showed 3 patients with plasma metformin concentrations among the highest seen in this series not to have lactic acidosis. It has also been shown in patients with chronic renal failure that metformin accumulation does not necessarily lead to lactic acidosis.[13] This implies that factors other than metformin accumulation are involved in the development of this condition, and that it is these factors that ultimately determine the prognosis. Indeed, there are no known cases of fatal lactic acidosis due to metformin alone.

Further interesting information is provided by analysis of the patients from study 2 with metformin accumulation and severe lactic acidosis (arterial pH below 7.0) who survived. These patients (most of whom also had circulatory shock) were clinically extremely unwell. Their unexpected survival gives rise to the challenging and provocative premise that high plasma concentrations of metformin might have protective effects (table III).

2. Metformin and Phenformin: Biguanides with Differing Characteristics and Properties

Metformin and phenformin are structurally distinct drugs, and these differences account for their different biochemical effects. Phenformin is associated with a well defined hyperlactataemic effect,[2] whereas metformin is characterised by a small increase in blood lactate levels, most noticeably after meals.[14,15] This is accompanied by small but significant elevations in circulating levels of the other gluconeogenic precursors pyruvate and alanine.[14] Phenformin's hyperlactataemic effect is caused by its physicochemical and biochemical properties: the drug has a long lipophilic side chain that causes it to bind to mitochondrial membranes (thereby inhibiting the electron transport system at the cell membrane level) and to be metabolised by aromatic hydroxylation in the liver.[16] This results in decreased lactate oxidation and increased lactate release from skeletal muscle. In contrast, metformin (dimethylbiguanide) is bisubstituted with 2 small groups that confer less lipophilicity on the molecule.[17] As a consequence, metformin is poorly bound to mitochondrial membranes, does not inhibit oxidative phosphorylation or influence lactate turnover or oxidation in either basal or insulin-stimulated states,[18] and does not undergo metabolic transformation.[17] Thus, metformin does not increase lactate production in skeletal muscle,[5] and any metformin-related increase in blood lactate levels does not arise from peripheral tissues. Data indicate instead that metformin increases lactate production via the extrahepatic splanchnic bed,[19] with animal studies favouring the small intestine as the site of origin.[20] The magnitude of this effect is known to be small when the drug is prescribed appropriately.[17]

Table III. Biochemical data from the patients of study 2[9] with severe lactic acidosis, high plasma metformin concentrations and survival

Arterial pH	Arterial lactate level (mmol/L)	Plasma metformin concentration (mg/L)
6.66	25.0	64.2
6.94	15.9	57.0
6.87	35.5	8.8
6.77	29.0	63.4
6.80	13.0	24.6
6.72	14.5	54.6
6.95	13.1	39.1

3. A Hypothesis for Beneficial Effects of Metformin Accumulation

Infusions of phenformin have been shown to decrease cardiac output and to increase left ventricular end diastolic pressure to a significant extent ($p < 0.01$).[21] In contrast, metformin has been associated with improvements in vascular function in patients with peripheral arterial disease[22,23] and in an animal model.[24] Montanari et al.[23] showed a 30% increase in peripheral blood flow with rather low dosages of metformin, in addition to significant increases in exercise capacity as assessed by the treadmill technique. It was suggested after experiments in hamsters with haemorrhagic shock that improvements in vasomotility underlie this beneficial effect.[24] Metformin was associated with increases in arterial vasomotility with accompanying increases in mean arterial blood pressure and, ultimately, improvements in rates of survival.

If hyperlactataemia is dangerous, it is because lactate excess results from tissue damage and hypoxia. Indeed, lactate in itself is not a toxic substance. Moreover, lactate substitutes directly for glucose as a metabolic substrate through entry via pyruvate into the tricarboxylic acid cycle. It has been consistently shown that intravenous lactate infusions prevent cerebral dysfunction during hypoglycaemic episodes in healthy volunteers[25] and patients with type 1 (insulin-dependent) diabetes.[26] Lactate infusion reduces autonomic and neurological symptom scores, and attenuates the deterioration in cognitive function.

It is therefore possible to identify 2 scenarios for lactic acidosis: that caused by disease in the absence of metformin accumulation and that linked to both metformin accumulation and concurrent disease. It can be stated on the basis of the above arguments that, for similar arterial lactate levels in these 2 situations, high plasma metformin concentrations are associated with less serious concurrent disease and, therefore, a better prognosis. It may also be hypothesised that, for a given severity of concurrent disease, higher plasma metformin concentrations are likely to be linked to better prognosis.

4. Implications for Treatment of Type 2 Diabetes

Assessment of the risk of adverse events is an important consideration in any management programme in type 2 (non–insulin-dependent) diabetes. From our point of view, metformin should be contraindicated in severe renal or hepatic failure. However, our findings suggest that metformin is not in itself a toxic agent with respect to hyperlactataemia, and that the risk-benefit ratio of diabetes treatment should be re-evaluated in the light of these findings. Unlike the sulphonylureas, metformin is not associated with hypoglycaemia or bodyweight gain. Indeed, a recent double-blind randomised study in obese patients with type 2 diabetes has shown metformin to reduce bodyweight in a dosage-dependent manner,[27] and there is evidence of beneficial vascular effects of metformin in animals and humans. In addition, the question of whether sulphonylureas may aggravate hypoxaemic myocardial damage in coronary occlusion or coronary artery disease through their effects on cardiac ATP-sensitive potassium channels[28,29] and whether this might explain the difference in mortality risk reduction between metformin and sulphonylureas in the United Kingdom Prospective Diabetes Study (UKPDS)[30] is still debated.

5. Conclusions

In conclusion, these data suggest that the degree of lactataemia has no adverse prognostic significance in lactic acidosis associated with metformin therapy, in contrast to that associated with other causes. Furthermore, unlike phenformin, accumulation of metformin appears not to have any prognostic significance. The likelihood of death appears rather to depend on the severity of any underlying hyperlactataemic condition that might be present. The data presented here are likely to be relevant to the management of older patients with type 2 diabetes, as the mean age of patients in study 2 was 68 years. Although it is too early to recommend broad guidelines for the continuation of

metformin therapy, our results indicate that treatment may be continued in older patients as long as the dosage is adjusted to reflect renal function.[31]

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