ORIGINAL RESEARCH ARTICLE

Drug Safety 1999 Apr; 20 (4): 377-384
0114-5916/99/0004-0377/$04.00/0

Lactic Acidosis in Metformin-Treated Patients

Prognostic Value of Arterial Lactate Levels and Plasma Metformin Concentrations

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Abstract

Objective: The antidiabetic drug metformin has been associated in a small number of patients with lactic acidosis, a serious condition with a poor prognosis. However, because of lack of data, the prognostic significance of hyperlactataemia in metformin-treated patients is not known.

Methods: Data were collected from 49 metformin-treated patients with lactic acidosis (arterial lactate level ≥5 mmol/L and blood pH ≤7.35) and available plasma metformin concentration data to investigate the association of arterial lactate levels and plasma metformin concentrations with mortality.

Results: The overall mortality rate in this patient sample was 45% and the median arterial lactate level was 13.1 mmol/L. Median lactate levels were similar in patients who survived (13 mmol/L) and those who died (14.3 mmol/L), whereas the median plasma metformin concentration was 3 times higher in patients who survived (20.6 mg/L versus 6.3 mg/L).

Conclusion: In this, the largest series of metformin-treated patients with lactic acidosis yet reported, 55% of patients survived and these patients had a median arterial lactate level of 13.1 mmol/L. Neither arterial lactate levels nor plasma metformin concentrations were of prognostic significance in relation to mortality in this sample of metformin-treated patients with lactic acidosis. Death in these patients appeared instead to be associated with other hypoxic disease or underlying ill health. These observations suggest that accumulation of metformin may not be as significant with respect to high arterial levels of lactate and their effects as has been traditionally thought.

It has been recognised for many years that lactic acidosis is associated with a high rate of mortality (30 to 50%) in critically ill patients.[1] Retrospective and prospective studies have consistently shown that, in patients with this metabolic condition, rates of survival fall dramatically when blood lactate levels exceed approximately 4 mmol/L.[2-4]

Metformin and phenformin are biguanide agents used as oral antihyperglycaemic agents in the treatment of type 2 (noninsulin-dependent) diabetes mellitus.[5] Metformin was introduced in 1957 and has enjoyed many years of widespread clinical use. Phenformin, however, was withdrawn in 1977 because of its association with a high inci-

dence of lactic acidosis. Metformin has also been linked with this metabolic disorder, but with an incidence 10 to 20 times lower than that seen with phenformin.[1,6] However, the link between plasma concentrations of metformin and lactic acidosis has not been clearly defined, and other precipitating factors (e.g. any illness likely to cause increased lactate production and/or defective lactate elimination) may be present in some patients.

The overall mortality rate in patients who develop lactic acidosis while receiving metformin has been estimated to be approximately 50%.[7] With the exception of a single study in 14 patients,[8] however, the influence of the degree of accumulation of metformin in plasma on the prognosis of hyperlactataemia has not been investigated. Therefore, in an attempt to clarify prognostic factors in patients receiving metformin who develop lactic acidosis, we have undertaken a retrospective analysis of metformin-treated patients in which plasma lactate levels and metformin concentrations were related to final outcomes.

Methods

Criteria for entry into the study were occurrence of lactic acidosis (arterial lactate level ≥5 mmol/L and arterial pH ≤7.35) during metformin therapy and availability of a plasma metformin concentration measurement. Arterial lactate levels and plasma metformin concentrations were plotted as a function of early mortality (defined as death before discharge from the intensive care unit).

Data Collection

Data were obtained from patients reported to the French National Drug Adverse Effect Surveillance Commission and from whom blood samples were sent to the pharmacokinetics laboratory of Le Havre Hospital, France, for determination of plasma concentrations of metformin.

Analytical Techniques

Arterial lactate levels were measured in each centre by an enzymatic method with standard automated techniques. Plasma metformin concentrations were measured in duplicate in the same laboratory with high-performance liquid chromatography in accordance with the method of Lacroix et al.[9] 50µl of plasma were injected into a cation exchange column (particle size 10µm, 250 × 4.6mm; SCX, Whatman) equilibrated with 100 mmol/L ammonium phosphate at a flow rate of 3 ml/min. The eluent was monitored using ultraviolet absorption at 232nm. Results were expressed as metformin base. Detection limits were 0.02 mg/L. The intra-assay coefficients of variation were 8.2% at 1.6 mg/L, <5% for the range 3 to 50 mg/L, and 5.7% at 100 mg/L; the inter-assay coefficients of variation were 11.2% at 1.7 mg/L and 6.7% at 19 mg/L. A standard mean fasting plasma metformin concentration (±2 standard deviations) of 0.6 ± 0.5 mg/L was adopted as being descriptive of patients receiving long term and well tolerated metformin therapy within the recommended dosage range and in the absence of renal failure.[8]

Description of Lactate Levels and Metformin Concentrations

In a previous series of metformin patients with lactic acidosis,[8] arterial lactate levels and plasma metformin concentrations varied widely between patients. In this series of patients, the range was 7.6 to 28.1 mmol/L for lactate and 0.03 to 84.9 mg/L for metformin, with a striking difference between median (7.75 mmol/L) and mean (23.2 mmol/L) lactate levels.[8] Median values for lactate and metformin are therefore presented in the present report.

Results

The main clinical and biochemical characteristics of the patients studied are shown in tables I and II. In these 49 patients (26 men), the mean age was 68 (range 42 to 86) years. Each patient had at least 1 risk factor for lactic acidosis, such as organ failure, sepsis or haemorrhage. Renal failure, either chronic or acute, was the predominant feature (36 out of 49 patients; 73%). Two or more risk factors were present in more than half of the patients (27 out of 49 patients).

Table I. Patient details and main clinical characteristics

Patient no.	Age	Gender	Chronic renal failure	Acute renal failure	Cardiovascular failure	Sepsis	Haemorrhage	Hepatic failure	Pulmonary failure
1	73	M	+						
2	80	F			+				
3	60	M		+	+				
4	62	F		+					
5	57	M		+		+			+
6	61	M		+	+				
7	60	F		+		+		+	
8	80	F		+					
9	42	F		+					
10	72	F							+
11	45	M	+		+				+
12	66	M						+	
13	79	M	+						
14	76	F	+	+				+	
15	72	M		+	+				
16	51	F		+					
17	61	F		+					
18	80	F		+			+		+
19	59	M		+				+	
20	59	M	+						
21	74	F		+					+
22	82	F	+		+			+	
23	75	M		+			+		
24	75	M		+	+				
25	60	M						+?	
26	58	F	+		+				
27	67	F		+	+	+			
28	69	F		+	+				
29	79	F			+	+	+		
30	76	M		+					
31	79	M		+					
32	68	M		+	+			+?	
33	82	M	+		+				
34	62	M		+					
35	86	M		+					+
36	65	F			+	+			
37	66	F		+					
38	54	M						+	
39	54	M		+				+	
40	74	M					+	+	
41	79	M					+	+	
42	69	M	+					+	
43	60	F				+			
44	67	F	+	+					
45	61	M						+	
46	67	F		+					
47	58	M				+		+	
48	80	F		+	+		+		+
49	69	F					+		
Total (%)			12 (24.5)	**28 (57.1)**	**15 (30.6)**	**7 (14.3)**	**7 (14.3)**	**12? (24.5?)**	**7 (14.3)**

F = female patient; **M** = male patient; **+** indicates presence of attribute.

Table II. Metformin dosages, concomitant sulfonylurea therapy, blood/serum parameters and mortality

Patient no.	Metformin dosage (g/day)	Concomitant sulfonylurea therapy	Blood glucose level (mg/dl)	BUN level (mg/dl)	Serum creatinine level (mg/dl)	pH	Lactate level (mmol/L)	Plasma metformin concentration (mg/L)	Death
1					2.8		17.6	6.8	Yes
2		Yes	698		0.8	7.13	12	4.4	Yes
3						6.66	25	64.2	No
4	3.4					7.24	12.7	25.2	No
5	2.55				6.7	7.23	20	22.5	No
6	1.7	No	123	234	22.6		7.9	46	No
7	2.55	No	306	107	4.3	6.88	11.8	23	Yes
8	2.55	Yes	198			7.24	5.9	59.6	No
9	2.55	No	142	151	11.3	7.03	30	80	Yes
10	0.85	Yes	542	73	1.5	6.93	10.8	0.8	Yes
11	2.55	Yes	11		10.7	6.94	15.9	57	No
12	3.4			127	2	7.23	17.2	2.2	Yes
13				155	6.6	7.34	7	13	No
14	1.7					7.24	9.8	37	Yes
15	1.7	No	432	175			8.8	4.4	No
16	1.7	Yes	256		5.7	6.99	26	23.7	Yes
17	1.7	Yes	11		8	7.01	28	68	No
18	1.7				5.6	7.21	7.9	12.6	No
19	2.55	Yes	355		4.6	6.87	35.5	8.8	No
20	2.55			167	9.7	6.77	29	63.4	No
21	3.4	No	130		9	6.6	14	107.3	Yes
22	2.5	Yes	5		7.9	7.24	6.7	25.5	No
23	1.7	No	200	244	3.8	7.11	17	9.9	No
24	2.55			175	8.5	6.89		60.3	Yes
25	1.7	Yes	57		8.8	6.4	15.4	5.8	Yes
26		Yes	57		3.8	7.17	7	7.9	No
27	1.7				10.2	6.8	13	24.6	No
28	1.7	No	151	114	2.3	7.24	7.6	7.6	No
29	1.7	Yes	450	49	2.2	7.21	9	0.03	Yes
30	1.7	No	73	130	4.4	7.34	11.5	8.9	No
31	0.85	No	103	180	8.4	7.07	11.6	42.9	Yes
32	3.4	Yes	268	139	9.2	6.72	14.5	54.6	No
33	1.7			322	6.5	7.14	15	24.5	Yes
34	2.55	Yes	22		8.9	7.29	8.1	20.6	No
35	1.7	No	472	975	6.2	7.2	22	28	Yes
36	1.7	Yes	660	128	3		11.9	0.6	Yes
37	1.7	Yes	231	207	3.9	6.99	20.8	14.8	No
38		Yes	595	25	1	6.63	14.3	1.9	No
39	2.55			168	10.6	6.58	25	62.9	Yes
40	1.7	Yes	345	129	1.4	6.97	12.1	2.2	Yes
41	1.7	No	569		2	6.86	28	0.7	Yes
42	1.7	Yes	218	110	2.3	7.3	5.8	2.8	No
43	0.5			136	3.2	7.25	14.5	3.7	Yes
44	1.7	Yes	687		7.6	6.95	13.1	39.1	No
45		No	504	58	3.9	7.09	16.3	0.4	No
46	3.4			145	6.7	7.27	9	23.5	No
47	2.55	No	276	80	1.3	7.13	>13	0.2	Yes
48	1.7				8.2	7.20	17	16.8	No
49	2.55			72	1.8	7.23	11.1	4.6	Yes

BUN = blood urea nitrogen.

The daily dose of metformin was known for 42 patients. Only 1 patient was receiving a low dosage (0.5 g/day), and 5 were receiving a high dosage (3.4 g/day). All others were receiving the recommended metformin dosage of 0.85 to 2.55 g/day. Random blood glucose levels varied widely, with the lowest values being recorded in patients who were receiving sulphonylureas in addition to metformin.

Blood pH values were not available for 4 patients, but these were classified as meeting the criterion for lactic acidosis on the grounds of very high plasma lactate levels (17.6, 7.9, 8.8 and 11.9 mmol/L). A plasma lactate value was missing in 1 patient, but this patient was judged to be hyperlactataemic on the grounds that his blood pH level was abnormally low (6.89). The median lactate level across all patients was 13.1 mmol/L (range 5.8 to 35.5 mmol/L), and hyperlactataemia was associated with overt acidaemia, the median arterial pH being 7.11 (range 6.4 to 7.4). The median plasma metformin concentration was 16.8 mg/L (range 0.03 to 107 mg/L); 6 patients had plasma metformin concentrations below 1 mg/L (at or below the level for the recommended dosage). In contrast, 8 patients had plasma metformin concentrations of at least 60 mg/L (i.e. 100 times the recommended level).

The overall mortality rate in these patients was 45% (22 of 49 patients). Median arterial lactate levels and plasma metformin concentrations are presented as a function of survival or mortality in figure 1. There was no difference in median arterial lactate levels between patients who survived (13 mmol/L) and those who died (14.3 mmol/L), whereas the median plasma metformin concentration was 3 times higher in the surviving patients (20.6 *vs* 6.3 mmol/L). Patients with the lowest plasma metformin concentrations (≤1 mg/L) appeared to have the poorest prognosis (only 1 of these 6 patients recovered).

Figure 2 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 (up to 35.5 mmol/L), the highest arterial lactate levels were seen in patients who survived.

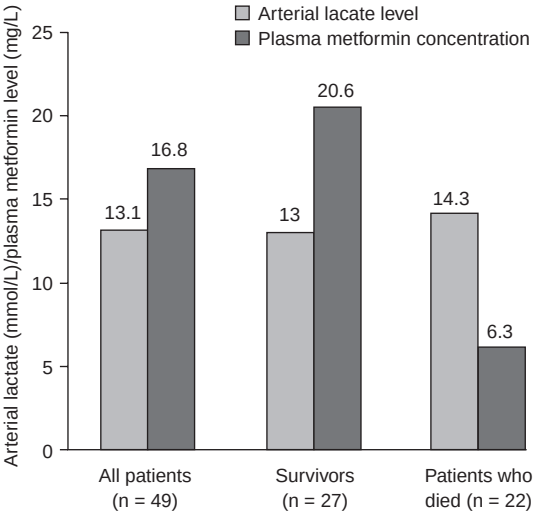

Fig. 1. Arterial lactate levels and plasma metformin concentrations shown as a function of outcome in 49 patients with lactic acidosis.

Discussion

In this, the largest series of metformin-treated patients with lactic acidosis yet reported, 55% of patients survived and these patients had a median arterial lactate level of 13.1 mmol/L. Importantly, a better prognosis was not associated with less severe hyperlactataemia; not only were median arterial lactate levels similar between patients who survived and those who died, but the distribution of lactate levels above the median was similar for the 2 groups. Furthermore, patients with arterial lactate levels as high as 35.5 mmol/L survived. Better prognosis was also not related to the degree of metformin accumulation; this was shown by the high rate of mortality in the patients with the lowest plasma concentrations of the drug.

It is not easy to explain the apparent contrasts between the above findings and the clinical course

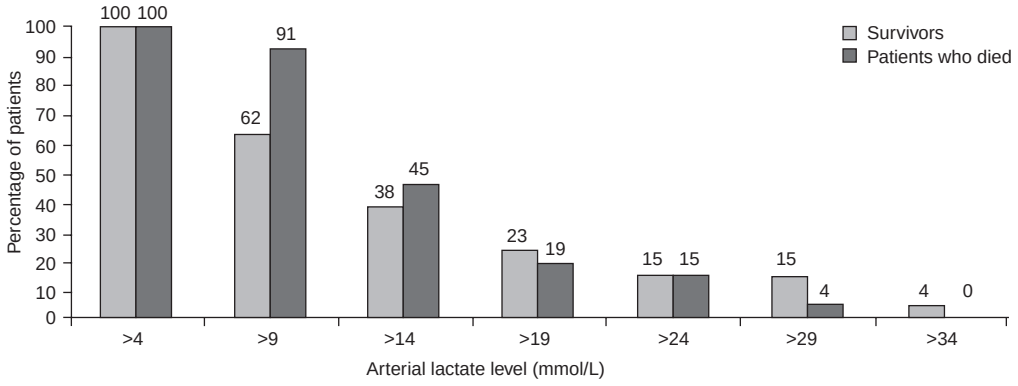

Fig. 2. Distribution of arterial lactate levels in patients with lactic acidosis who survived and those who died.

of lactic acidosis caused by phenformin or by underlying disease. Diseases that result in lactic acidosis are usually extremely serious (e.g. cardiac failure, hypoxaemia, sepsis, hepatic failure), and it is therefore not surprising that the prognosis is poor for affected patients.[2,4,10] It should be noted that all patients studied in the present series had at least one medical condition that could provoke hyperlactataemia.

The effects of biguanides on lactate metabolism must also be understood for a clear appreciation of the pathogenesis of biguanide-associated lactic acidosis. Phenformin is associated with a well defined hyperlactataemic effect,[11] whereas metformin is characterised by a small increase in blood lactate levels, most noticeably after meals.[12,13] This is accompanied by small but significant elevations in circulating levels of the other gluconeogenic precursors, pyruvate and alanine.[12] The hyperlactataemic effect of phenformin is caused by its physicochemical and biochemical properties: the drug possesses 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.[14] 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.[5] As a consequence, metformin is poorly bound to mitochondrial membranes, does not inhibit oxidative phosphorylation or influence lactate turnover or oxidation in either the basal or insulin-stimulated state,[15] and does not undergo metabolic transformation.[5] Thus, metformin does not increase lactate production in skeletal muscle,[1] and any metformin-related increase in blood lactate levels does not arise from peripheral tissues. Instead, data indicate that metformin increases lactate production via the extrahepatic splanchnic bed,[16] with animal studies favouring the small intestine as the site of origin.[17] The magnitude of this effect is known to be small when the drug is prescribed appropriately.[5]

The presence of lactic acidosis during metformin treatment is normally attributed to high plasma drug concentrations caused by renal failure or overdosage, (circulating plasma concentrations of metformin should not normally exceed 5 mg/L[1]) the coexistence of an underlying disease that predisposes to or causes hyperlactataemia, or a combination of the 2. Classically, lactic acidosis is subdivided into type A (caused by tissue hypoxia) and type B (caused by lactic acid overproduction and/or defective excretion in the aerobic state).[18] Biguanide-induced lactic acidosis is classified as type B, and is the reason behind the contraindications to metformin therapy. Indeed, lactic acidosis with metformin therapy has been stated to

occur exclusively in patients with contraindications to the drug's use, which leads to the supposition that this adverse effect might be avoided through strict adherence to prescribing guidelines.[1] However, data from an earlier study[8] indicated that pure type B (aerobic) lactic acidosis occurs only in exceptional cases and that most metformin-treated patients present with a mixed (A + B) lactic acidosis (i.e. metformin accumulation with concurrent disease). There are therefore 3 possible clinical scenarios in patients with lactic acidosis who have received metformin: (i) lactic acidosis that is not related to metformin (i.e. in the absence of accumulation of metformin); (ii) lactic acidosis in the presence of marked metformin accumulation but with no other associated factors besides renal failure (necessary for accumulation of the drug); and (iii) lactic acidosis associated with metformin accumulation and a relevant pathological condition.

In the 6 patients with low plasma metformin concentrations in this study (i.e. those in whom lactic acidosis was deemed to be unrelated to metformin), a high mortality rate was recorded (only 1 of these patients recovered). This is perhaps not surprising, as clinical disorders that cause lactic acidosis through diminished tissue oxygenation are serious and frequently life-threatening. In those patients with lactic acidosis that was linked with metformin accumulation, a low mortality rate was observed: of the 12 patients with renal failure accompanied by plasma metformin concentrations above 10 mg/L and no other associated precipitating factors (apart from renal failure), only 3 died. It should be noted that the absence of a precipitating factor does not necessarily imply sound underlying health status on the part of the patient; 1 of the 3 deceased patients in this group had severe peripheral vascular disease, invasive bladder cancer and a urinary tract infection. It is possible that patients with lactic acidosis secondary to metformin accumulation alone do indeed have a relatively good prognosis because, as stated earlier, metformin-induced hyperlactataemia does not result from the inability of peripheral tissues to meet metabolic demand but originates from the small intestine, which normally exhibits a high rate of anaerobic glucose metabolism.

An intermediate prognosis was observed in patients with both metformin accumulation and other predisposing conditions. Of 18 patients with plasma metformin concentrations of at least 10 mg/L and coexisting hyperlactataemic disease, 7 died. The prognosis in these patients appeared to depend not upon the degree of hyperlactataemia or metformin accumulation but upon the severity of other underlying diseases. It also appears that, for a given level of arterial lactate, higher plasma concentrations of metformin are associated with a better prognosis. These data are concordant with earlier observations in patients with lactic acidosis in whom survival appeared not to be linked to metformin accumulation and whose prognosis was dependent on the severity of coexisting pathological conditions.[8]

Since increased plasma concentrations of metformin without coexisting severe illness predisposing to hyperlactataemia were not associated with increased mortality in the present study, it may be postulated that the link between metformin and death caused by high arterial levels of lactate is not as clear as previously thought and requires further investigation. This also gives rise to the challenging and provocative premise that high plasma concentrations of metformin might have beneficial effects. Indeed, data are available in patients with peripheral arterial disease to show significant improvements in vascular function after treatment with metformin 500mg twice daily or 850mg 3 times daily.[19,20] It has been suggested after experiments in hamsters with haemorrhagic shock that improvements in vasomotility underlie this beneficial effect.[21] Metformin was associated with increases in arterial vasomotility with accompanying increases in mean arterial blood pressure and, ultimately, improvements in rates of survival. In the light of these observations, it may be hypothesised that beneficial effects on vascular function might account for the survival of patients

in this study with clinical shock and those with the highest arterial lactate levels (up to 35.5 mmol/L).

Finally, it should be noted that metformin is a antihyperglycaemic rather than a hypoglycaemic agent under conditions of either normal therapeutic use or massive accumulation; accordingly, hypoglycaemia was recorded only in patients with concomitant sulfonylurea therapy.

Conclusion

In conclusion, these data suggest that the degree of lactataemia has no 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 be dependent upon the severity of any underlying hyperlactataemic condition that might be present (bearing in mind particularly that the patients involved in this study had a mean age of 68 years). These findings suggest that the association between accumulation of metformin in the plasma (normally caused by renal failure) and mortality with high arterial lactate levels may not be as straightforward as has been believed. Indeed, in the light of these findings and what is known about the mechanisms by which arterial lactate levels are increased, it is even possible that metformin had no clinically significant hyperlactataemic effect in these patients. As the risk of adverse effects is an important consideration in drug treatment decisions, these findings are likely to be highly relevant to the management of type 2 diabetes mellitus, particularly where elderly patients are concerned.

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