Role of Metformin Accumulation in Metformin-Associated Lactic Acidosis

JEAN D. LALAU, MD, PHD
CHRISTIAN LACROIX, MD
PATRICIA COMPAGNON, MD
BERTRAND DE CAGNY, MD
JEAN P. RIGAUD, MD
GÉRARD BLEICHNER, MD
PAUL CHAUVEAU, MD
PATRICIA DULBECCO, MD
CLAUDE GUÉRIN, MD
JEAN M. HAEGY, MD
PHILIPPE LOIRAT, MD
BRUNO MARCHAND, MD
YVES RAVAUD, MD
PHILIPPE WEYNE, MD
ALBERT FOURNIER, MD

OBJECTIVE — To investigate the role of metformin accumulation in the pathophysiology of metformin-associated lactic acidosis.

RESEARCH DESIGN AND METHODS — We used high-performance liquid chromatography to measure plasma metformin concentrations in 14 patients who experienced lactic acidosis (pH <7.35 and lactate concentration >5 mmol/l) while receiving chronic metformin treatment. Their treatment was generally based on alkalinization and dialysis therapy.

RESULTS — Clinical shock and/or evidence of tissue hypoxia was found in all patients with the exception of one who had a nonsteroidal anti-inflammatory drug–induced anuria. Ten patients had significant metformin accumulation (plasma metformin concentrations 4.1–84.9 mg/l, normal value 0.6 ± 0.5 mg/l before drug intake), generally because of failure to withdraw metformin despite intercurrent pathological conditions affecting its renal elimination (serum creatinine concentrations ranging from 269 to 1,091 μmol/l). There was no metformin accumulation (plasma metformin 0.03–0.7 mg/l) in the four other patients, who had less severe renal failure (serum creatinine 140–349 μmol/l). The severity of the patient's general condition did not predict early hospital mortality (death before discharge from the intensive care unit) even in patients in shock. Whereas it was high in those without metformin accumulation (only 1 of 4 patients recovered), early hospital mortality was low in the 10 patients with metformin accumulation and was not related to its extent (3 patients died with end-stage hepatic failure or cardiac failure). Correlation studies showed a positive correlation between serum creatinine and plasma metformin and between plasma metformin and arterial lactate but, for the latter correlation, only in patients with metformin accumulation.

CONCLUSIONS — Metformin-associated lactic acidosis is not necessarily due to metformin accumulation; true type B (aerobic) lactic acidosis, i.e., without an apparent associated hypoxic factor, seems exceptional. Neither the severity of the clinical picture nor the degree of metformin accumulation predicted survival; rather, the prognosis was dependent upon the severity of the associated pathological conditions.

From the Service d'Endocrinologie (J.D.L.) and the Service de Néphrologie-Réanimation (B.D.C., A.F.), Hôpital Universitaire, Amiens; the Laboratoire de Pharmacocinétique (C.L.) and the Service de Réanimation (J.P.R.), Centre Hospitalier, Le Havre; the Laboratoire de Pharmacologie (P. Compagnon), Hôpital Universitaire, Rouen; the Service de Réanimation Polyvalente (G.B.), Centre Hospitalier, Argenteuil; the Service de Réanimation Polyvalente (P. Chauveau), Centre Hospitalier Intercommunal, Montreuil; the Service de Réanimation (P.D.), Centre Hospitalier, Antibes; the Service de Néphrologie (C.G.), Hôpital Universitaire, Saint-Etienne; the Service d'Urgences et de Réanimation (J.M.H.), Centre Hospitalier, Colmar; the Service d'Urgences et de Réanimation (P.L.), Centre Médico-chirurgical, Foch; the Service d'Anesthésie-Réanimation (B.M.), Centre Hospitalier, Lagny; the Service de Réanimation Polyvalente (Y.R.), Hôpital des Diaconesses, Paris; and the Service d'Anesthésie-Réanimation (P.W.), Centre Hospitalier, Montbrison, France.

Address correspondence and reprint requests to Jean D. Lalau, MD, Hôpital Sud, 80054 Amiens Cédex 1, France.
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MALA, metformin-associated lactic acidosis.

Metformin (1,1-dimethylbiguanide) is widely prescribed for the treatment of non-insulin-dependent diabetes. Its association with lactic acidosis is well established, although rare (1,2). Metformin-associated lactic acidosis (MALA) is still considered a very serious condition with a poor prognosis. The overall mortality rate is estimated to be ~50% (3,4).

In contrast with the renewed interest in the metabolic effects of metformin (5–7), there are few articles discussing the pathophysiology of MALA. Lactic acidosis is classically differentiated into two varieties: anaerobic (type A) and aerobic (type B) (8,9). The hallmark of type A lactic acidosis is tissue hypoxia resulting in anaerobic lactic acid production. In type B lactic acidosis, lactic acid production is increased in the absence of overt hypoxia. MALA is generally assumed to be a type B lactic acidosis resulting from metformin accumulation (8,9). The main cause of metformin accumulation is renal failure, since metformin is eliminated unchanged by the kidney exclusively (1,10). However, with the exception of a few single case reports, metformin accumulation leading to elevated plasma levels has been documented only in one series of four MALA patients (11) and in one series of diabetic patients with hyperlactatemia but not necessarily acidosis (12). Moreover, the link between plasma metformin accumulation and type B lactic acidosis necessitates that there is no pathological factor besides metformin accumulation. Therefore, to better delineate the causal role of metformin accumulation in triggering MALA, we measured plasma metformin concentrations in 14 patients with MALA. Our data are discussed with respect to the severity of the lactic acidosis and the coexistence of clinical hypoxic factors.

RESEARCH DESIGN AND METHODS

Selection of patients

Blood samples from patients at risk for MALA were sent from 14 intensive care

units to the pharmacokinetics laboratory of Le Havre Hospital for determination of the plasma concentration of metformin. From this series, over a period of 4 years 14 patients were identified as having MALA. Lactic acidosis was defined, according to the criteria of Luft et al. (13), as a blood pH <7.35 and a concentration of lactate in arterial blood >5 mmol/l. If available, information about the time elapsed between the last metformin intake and the blood sampling for metformin determination and the value for the last routine serum creatinine measurement determined before admission were reported.

Plasma metformin concentrations were studied in the 14 MALA patients and compared with those obtained in the fasting state in 58 diabetic patients receiving well-tolerated chronic metformin treatment at the recommended dosage (1,700–2,550 mg/day). These patients with stable diabetes were aged 55.2 ± 1.6 years (range 30–80 years). They had no renal failure (serum creatinine 74 ± 3 μmol/l [mean ± SD]) and no significant hyperlactatemia (arterial lactate concentration 1.09 ± 0.06 mmol/l, highest value <2.4 mmol/l).

Treatment of MALA was generally based on alkalinization (intravenous administration of sodium bicarbonate, 10 patients) and dialysis (hemodialysis, 9 patients; hemofiltration, 2 patients).

Analytical methods

All blood samples were collected on admission or shortly thereafter. Creatinine was measured using an autoanalyzer (Astra, Worcester, MA). Arterial blood samples for lactic acid determination were rapidly centrifuged and deproteinized using 0.6 mol/l perchloric acid. Lactic acid was measured by an enzymatic method using an autoanalyzer (ACA, Du Pont, Wilmington, DE). Blood samples for metformin determination were collected into heparinized tubes and rapidly centrifuged and deproteinized by 10% trichloroacetic acid. Metformin was measured in duplicate in the same laboratory using high-performance liquid chromatography according to the technique of Charles et al. (14) modified by Lacroix et al. (15). Fifty microliters of plasma were injected onto a cation exchange column (10 μm, 250 × 4.6 mm; 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 232 nm. 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 3–50 mg/l, and 5.7% at 100 mg/l; the interassay coefficients of variation were 11.2% at 1.7 mg/l and 6.7% at 19 mg/l.

Statistical analysis

Results are presented as means ± 2 SD in diabetic patients receiving well-tolerated chronic metformin treatment and as means ± SE in MALA patients. In MALA patients, Wilcoxon's nonparametric test was performed to compare pH and lactate concentrations between patients with or without metformin accumulation. Correlation studies used least-squares regression.

RESULTS

Clinical and biological characteristics of the MALA patients

All MALA patients but two were ≥60 years old (mean 68.1 ± 2.3, range 54–79 years) (Table 1). Most patients (11 of 14) exhibited circulatory shock on admission or shortly thereafter. Only one patient had no apparent precipitating or predisposing factor for hypoxia (patient 2, with isolated anuria induced by a nonsteroidal anti-inflammatory drug).

Only one patient (patient 3) had been taking a rather high metformin dosage (3,400 mg/day); the others were receiving the recommended dosage (850–2,550 mg/day). This treatment was continued until admission in six patients.

Plasma metformin levels are presented in Table 1 in decreasing order. In comparison with the diabetic patients with well-tolerated chronic metformin treatment, who had plasma metformin concentrations of 0.6 ± 0.5 mg/l, 10 MALA patients exhibited metformin accumulation with a plasma metformin value >4 mg/l. The highest values (39–85 mg/l) were noted in patients 1–5, who continued the metformin treatment until admission and who had severe renal failure (serum creatinine 670–1,091 μmol/l) presumably of recent onset, except for patient 4 (with chronic obstructive uropathy). Patients 6–10 had metformin levels of 4.1–8.9 mg/l and less severe renal failure (serum creatinine 269–779 μmol/l). The four remaining MALA patients (patients 11–14) had no significant metformin accumulation: their plasma metformin concentrations were <1 mg/l, as low as or even lower than those in the group of diabetic subjects without MALA. These patients had mild renal failure (serum creatinine concentration 140–349 μmol/l).

Arterial pH and lactate concentrations were not statistically different between patients with or without metformin accumulation. In contrast, the early mortality (death before discharge from the intensive care unit) was quite different: in the 10 patients with metformin accumulation, death occurred only in the 3 patients with end-stage hepatic failure (patients 1 and 9) or cardiac failure (patient 10), while 3 of 4 patients without metformin accumulation died rapidly.

General conditions of MALA patients with shock

Table 2 gives some details about the severity of the general conditions of MALA patients with shock. Tissue hypoxia could not be determined and thus graduated, since most of these patients were receiving mechanical ventilation on admission. Consequently, the severity of the shock syndrome has been analyzed using some clinical variables and the need for inotropic drugs. Mortality (Table 1) did not correlate with the severity of the

Table 1—*Clinical and biological characteristics of patients with MALA*

Patient	Age	Sex	Clinical setting	Clinical shock	Creatinine (μmol/l)	Previous creatinine (μmol/l)	pH	Lactate (mmol/l)	Metformin treatment		Plasma metformin (mg/l)	Early mortality
									Dosage (g/day)	Withdrawal		
1	54	M	End-stage hepatic failure	Yes	1,037	88 (6 mo)	6.58	27.0	2.55	No	84.9	2 d
2	61	F	Drug-induced anuria	No	703	70 (8 d)	7.01	28.0	2.55	No	68.0	No
3	67	M	Dehydration-induced anuria	Yes	814	98 (4 d)	6.72	14.5	3.4	No	54.6	No
4	79	M	Arteriopathy, obstructive anuria	No	1,091	741 (6 d)	7.07	11.5	0.85	No	42.9	No
5	67	F	Postsurgical anuria	Yes	670	102 (3 d)	6.95	13.1	1.7	No	39.1	No
6	76	M	Myocardial infarction, sepsis	Yes	390	353 (1 d)	7.35	11.0	1.7	Yes (1 d)	8.9	No
7	58	F	Acute pulmonary edema	Yes	338	Abnormal	7.17	15.5	?	Yes (1 d)	7.9	No
8	69	F	Cardiac failure, arteriography	No	448	199 (4 d)	7.24	7.6	1.7	Yes (4 d)	7.6	No
9	60	M	End-stage hepatic failure	Yes	779	88 (2 d)	6.4	15.4	1.7	Yes (2 d)	5.7	3 d
10	75	M	Cardiac failure	Yes	269	177 (3 mo)	7.05	12.7	1.7	Yes (1 d)	4.1	4 d
11	79	M	Cirrhosis, hematemesis	Yes	172	?	6.88	28.1	1.7	Yes (?)	0.7	5 h
12	62	M	Hepatic failure, sepsis	Yes	349	Normal (1 d)	7.09	16.3	1.7	No	0.4	No
13	68	F	Myocardial infarction, sepsis	Yes	140	Normal	7.12	12.0	1.7	Yes (1 d)	0.2	1 h
14	79	F	Mesenteric infarction, sepsis	Yes	197	?	7.21	9.0	1.7	Yes (1 d)	0.03	2 d

Shown in parentheses are the delays in months (mo) or days (d) between admission and last routine determination of creatinine or last metformin intake. Early mortality indicates death that occurred rapidly after admission in hours (h) or days (d).

shock syndrome. Death occurred 6 times out of 11 no matter whether the patient's general condition was precarious or not; for example, patients 5 and 7, whose initial conditions were very bad, survived, while patients 11 and 14, whose initial conditions were less severe, ultimately died.

Results of correlation studies performed in MALA patients and in the group of diabetic subjects without MALA

In MALA patients taken as a whole, as well as in diabetic subjects without MALA, plasma metformin levels were correlated with serum creatinine but not with lactate concentrations (MALA patients: creatinine-metformin, $r = 0.81$, $P < 0.001$; lactate-metformin, $r = 0.50$, NS [Fig. 1]; diabetic patients without MALA: creatinine-metformin, $r = 0.42$, $P < 0.001$; lactate-metformin, $r = 0.21$, NS). For only the 10 MALA patients with metformin accumulation, plasma metformin

Table 2—*General condition of MALA patients with shock*

Patient	Consciousness	Skin perfusion	Mechanical ventilation	Hemodynamic status	Urine excretion	Inotropic drug(s)
1	Deep coma	Pathological	Yes	Cardiac arrest	Anuria	Yes
3	Drowsy	Pathological	Yes	Collapse	Anuria	Yes
5	Deep coma	Pathological	Yes	Collapse	Anuria	Yes
6	Drowsy	Normal	Yes	Collapse	Oliguria	Yes
7	Drowsy	Pathological	Yes	Cardiorespiratory distress	Oliguria	No
9	Deep coma	Pathological	Yes	Cardiorespiratory distress	Anuria	Yes
10	Normal	Pathological	Yes	Collapse	Oliguria	No
11	Drowsy	Normal	No	Normal (after fluids)	Normal	Yes
12	Drowsy	Normal	Yes	Collapse	Anuria	No
13	Normal	Pathological	Yes	Cardiac arrest	Oliguria	Yes
14	Normal	Normal?	Yes	Collapse	Oliguria	Yes

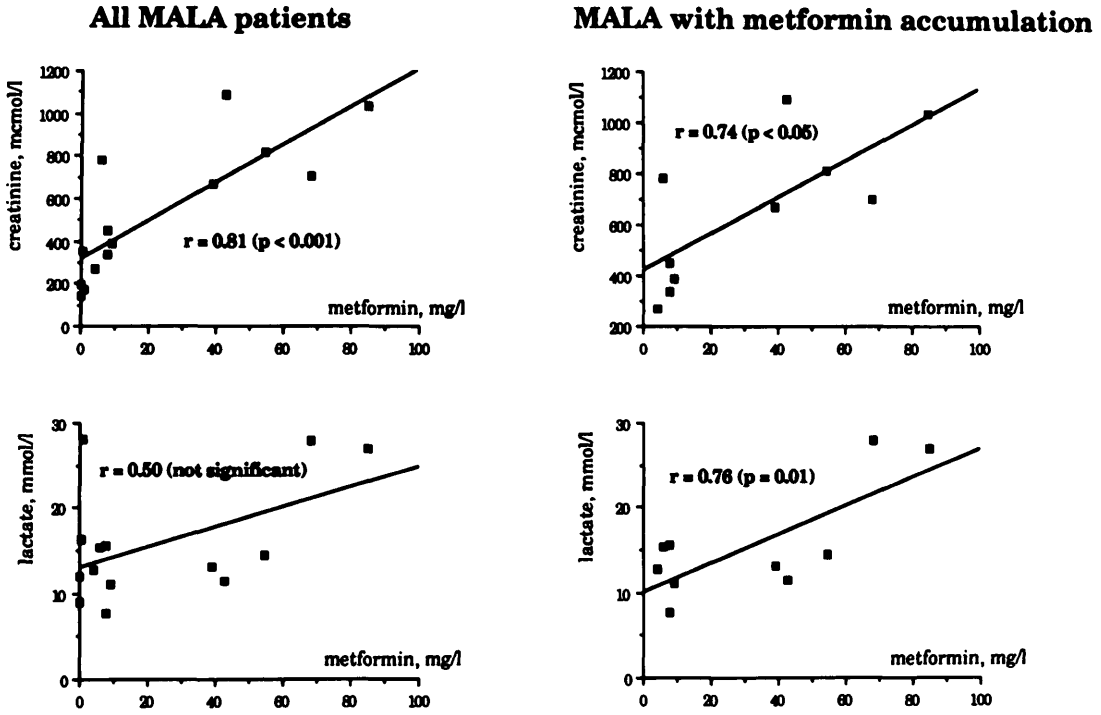

Figure 1 *Relationship between plasma metformin levels and plasma creatinine and lactate in patients with MALA. For all MALA patients* n = *14; for MALA patients with metformin accumulation* n = *10.*

levels were correlated not only with serum creatinine ($r = 0.74$, $P < 0.05$) but also with lactate concentrations ($r = 0.76$, $P = 0.01$) (Fig. 1).

The other correlation studies performed in the whole group of MALA patients showed a negative correlation between serum creatinine and arterial pH ($r = -0.56$, $P < 0.05$) and no correlation between lactate concentration and pH or serum creatinine ($r = -0.48$ and $r = 0.21$, respectively, NS).

CONCLUSIONS — Classically a distinction is made between type A lactic acidosis, due to tissue hypoxia, and type B, resulting from lactic acid overproduction for various reasons in an otherwise aerobic state (8,9). Examples of type B lactic acidosis include that induced by biguanides. From the occurrence of MALA, it cannot be inferred, however, that metformin is the causative agent without direct evidence of a significant accumulation of metformin.

This study clearly shows that the lactic acidosis in metformin-treated patients was not necessarily due to metformin accumulation, since in four cases there was no significant increase in plasma metformin. Lactic acidosis was thus related to one or more etiological factors independent of metformin. Moreover, although accumulation was demonstrated in the 10 other patients, this does not imply that metformin was solely responsible, since factors for hypoxia and/or clinical shock were present in all patients but one. The severity of these hypoxic factors rather than the extent of metformin accumulation actually determined the prognosis, since the prognosis was satisfactory in situations of metformin accumulation (with the exception of patients with associated diseases such as end-stage hepatic failure or cardiac failure), whereas the outcome was poor in the absence of metformin accumulation.

Since mortality did not correlate with plasma metformin levels, it is interesting to graduate tissue hypoxia and/or clinical shock to correlate with mortality. However, classic indexes used to graduate the severity of a shock syndrome involve variables such as temperature, respiratory rate, and arterial pH, which are affected by lactic acidosis per se whatever the underlying condition. Moreover, the measure of Pa_{O_2} could provide an index of tissue oxygenation, but this parameter was not available because all patients in shock but one were already under mechanical ventilation. Thus, it is preferable to give details about the general conditions of the patients in shock instead of an erroneous gradation of tissue hypoxia. Tables 1 and 2 show that mortality did not correlate with the severity of the shock syndrome, but actually with the severity of patients' underlying diseases (such as end-stage hepatic failure, cardiac failure, or sepsis).

Measuring plasma metformin allows the differentiation of three types of MALA: *1*) type A (anaerobic) lactic acido-

sis unrelated to metformin in four patients without metformin accumulation and with a poor prognosis; 2) type B (aerobic) lactic acidosis present in only one patient with marked metformin accumulation but no associated factors for hypoxia (patient 2) and with a satisfactory prognosis; and 3) a mixed type (A + B) of lactic acidosis in nine patients with both metformin accumulation and factors for hypoxia and with an intermediate prognosis. Since many pathological mechanisms may trigger and sustain hyperlactatemia (8,9), the identification of the mechanisms for the different types of lactic acidosis that we have distinguished is complex. Moreover, hyperlactatemia may be multifactorial for a given patient, being secondary to lactate overproduction because of tissue hypoxia, metformin accumulation, since metformin is known to directly enhance lactate production by the intestine (16,17), and defective lactate elimination because of primary renal or hepatic failure. Acidosis further aggravates hyperlactatemia because it hampers the hepatic clearance of lactate, and in severe acidosis, the liver becomes a lactate-producing organ (8). The fact that serum creatinine but not serum lactate concentrations were negatively correlated with pH suggests that the increase in lactate concentration was only one component of the acidosis, the others being more directly related to renal failure (decreased elimination of titratable acidity and ammonium).

It is noteworthy that in patients with metformin accumulation (type B and, most commonly, type A + B lactic acidosis), hyperlactatemia and acidosis were comparable to those in patients with type A lactic acidosis. Because of the effect of metformin on lactate production by intestine (16,17), the hyperlactatemia of patients with metformin accumulation was at least partly due to a direct effect of metformin and not only to tissue hypoxia. Effectively, lactate concentrations were correlated with metformin concentrations in those patients (compared with the whole group of MALA patients). Consequently, we can assume that for similar lactate levels in type A + B and type A lactic acidosis, the higher the degree of metformin accumulation, the less severe the hypoxia-related hyperlactatemia. This accounts for the difference in prognosis observed for these two situations.

The outcome cannot be predicted by the degree of hyperlactatemia; consequently, hyperlactatemia cannot be considered as a valid criterion for determining the prognosis of MALA with metformin accumulation. This is clearly shown by the fact that our 10 patients with metformin accumulation had arterial lactic acid levels >7.6 mmol/l (mean 15.6) and 7 showed clinical shock but most survived, whereas the literature reports that circulatory shock with a lactate level >4.4 mmol/l is associated with a mortality rate as high as 82% (18). Data from a recent report confirms these early findings (19). As a matter of fact, lactate overproduction has never been shown to be harmful per se (20).

Except for in metformin overdosage, renal failure is a prerequisite for metformin accumulation, since metformin elimination is dependent solely on renal function (1,10). With respect to this, the problem is knowing whether shock may be at least a contributor to metformin accumulation (because of shock-induced renal hypoperfusion). Considering the acute nature of renal failure, it is generally not evident from Table 1 that renal function was already seriously altered before admission. This suggests that metformin accumulation may occur relatively rapidly in relation to intercurrent pathological conditions affecting its renal elimination. However, anuria accompanying shock cannot lead very quickly to significant metformin accumulation, as shown by patient 12. This patient had no metformin accumulation despite a serum creatinine concentration of 349 μmol/l and no discontinuation of metformin treatment: he presented with shock on arrival because of ventricular tachycardia (due to hyperkalemia), although his blood urea nitrogen concentration was normal the day before admission. Thus, the metformin accumulation indicates that renal failure existed before shock, whatever its cause (organic renal failure or various conditions involving poor tissue perfusion). Therefore, we would stress finally that metformin accumulation cannot occur rapidly in relation to intercurrent pathological conditions affecting the renal elimination of metformin and should never be encountered if the classic contraindication, which is renal failure, is recognized.

In conclusion, the measurement of metformin concentrations in patients with MALA clearly shows that MALA should no longer be considered as a pure entity, since a clear-cut distinction may be made between three varieties of lactic acidosis: type A, unrelated to metformin (between one-fourth and one-third of cases); type B, with major metformin accumulation, which is exceptional (only one case); and a mixed type (A + B), with metformin accumulation and associated factors of hypoxia, which is the most common type. Neither the degree of metformin accumulation nor the severity of the initial clinical picture predicted survival; rather the prognosis was dependent upon the severity of associated pathological conditions.

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