

# Metformin-associated lactic acidosis (MALA): clinical profile and outcomes in patients admitted to the intensive care unit

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Metformin is a widely used antidiabetic agent for the treatment of type 2 diabetes mellitus. Metformin-associated lactic acidosis (MALA) is a serious but uncommon complication of metformin use and is reported to have a mortality rate of up to 45%.<sup>1,2</sup> Most studies have defined MALA as hyperlactataemia with acidaemia in the presence of metformin use. For the diagnosis of MALA, most studies have used a lactate threshold level of  $\geq 5$  mmol/L,<sup>1,2</sup> but some have used hyperlactataemia (level not defined) in combination with a plasma metformin level of  $>2$  mg/L.<sup>3</sup> The diagnosis of MALA is subject to debate, and it should be a diagnosis of exclusion after ruling out clinically common causes of lactic acidosis among metformin users.

The true incidence of MALA is unknown — a function, at least in part, of varying definitions. An incidence of 2.4 to 10 cases per 100 000 patient prescriptions per year has been reported in European and Canadian populations.<sup>4-6</sup> An Australian study has reported an incidence of 57 (95% CI, 12–168) per 100 000 patient-years in metformin-treated patients, with incidence increasing with age and duration of the diabetes as cardiovascular and renal complications become more prevalent.<sup>7</sup> A French study of MALA in an intensive care unit reported an incidence of 0.84% among all admissions to the ICU during the study, with a 28-day mortality of 30%.<sup>1</sup>

There is controversy about the precise role of metformin in the development of lactic acidosis. The Cochrane group, after analysing pooled data from all prospective comparative trials and observational cohort studies up to 2009, concluded that “there is no evidence from prospective comparative trials or from observational cohort studies that metformin is associated with an increased risk of lactic acidosis, or with increased levels of lactate, compared with other antihyperglycaemic treatments”.<sup>5</sup> The United Kingdom Prospective Diabetes Study of newly diagnosed type 2 diabetes compared patients treated with metformin alone versus diet alone or other hypoglycaemic agents and observed no deaths due to lactic acidosis.<sup>8</sup> Other cohort studies have demonstrated a very low incidence of MALA.<sup>9-11</sup> There also appears to be no correlation between metformin levels and lactate levels in patients with lactic acidosis.<sup>2,3,12-14</sup> Further, the Comparative Outcomes Study of Metformin Intervention versus Conventional Approach (COSMIC) study, which compared the outcome and therapeutic safety of metformin intervention

## ABSTRACT

**Background:** Metformin, a widely used hypoglycaemic agent in type 2 diabetes mellitus, is uncommonly associated with lactic acidosis, a serious condition with high mortality.

**Objective:** To evaluate the incidence of metformin-associated lactic acidosis (MALA) in an Australian intensive care unit, and the clinical profile and outcomes of patients admitted to the ICU with this diagnosis.

**Design, setting and participants:** We analysed data on patients admitted to a 14-bed tertiary care adult ICU over a 5-year period (January 2003 to December 2007). We did manual searches of ICU discharge summaries, reviewing case notes and cross-referencing with the ICU electronic database to identify and characterise patients with an ICU discharge diagnosis of MALA. MALA was defined as a syndrome of elevated blood lactate level with acidaemia in patients taking metformin (after other causes of lactic acidosis had been excluded).

**Results:** There were 17 patients in our study cohort, with a mean age of 65 (SD, 9.9) years. MALA was diagnosed in 6 per 1000 ICU admissions. All patients with MALA presented with gastrointestinal symptoms of nausea, vomiting and/or diarrhoea, and 11 had clinical signs of dehydration. Patients had evidence of severe acidosis (mean pH 6.92 [SD, 0.26]; anion gap, 34 [SD, 10]); high lactate levels (mean 9.6 [SD, 4.1] mmol/L); and acute renal dysfunction (mean creatinine level 585 [SD, 305]  $\mu$ mol/L). The mean APACHE (Acute Physiology and Chronic Health Evaluation) III score was 106.4 (SD, 42.9). The mean invasive mechanical ventilation time (for 13 patients who required ventilation) was 23.4 (SD, 32.3) hours, and mean ICU length of stay was 62.8 (SD, 53.5) hours. Thirteen patients required dialysis and vasopressor support and two had a negative laparotomy; 5/17 patients (29%) died. APACHE III score, arterial pH on admission and male sex were associated with an increased risk of death in hospital ( $P < 0.05$ ).

**Conclusion:** MALA is a not uncommon cause of ICU admission. Gastrointestinal symptoms predominate in MALA, and the condition is associated with significant morbidity and mortality.

Crit Care Resusc 2010; 12: 191–195

versus conventional therapy (other antidiabetic therapy excluding metformin), found that death and hospitalisation did not differ significantly between the groups and lactic acidosis was not observed in either group.<sup>9</sup> These observations have raised doubts about the pathogenic significance of MALA and have probably led to the change in terminology from metformin-induced lactic acidosis to metformin-associated lactic acidosis.

Nevertheless, frequent reports of "MALA" continue to be published. In 1996, the United States Food and Drug Administration received 47 reports of MALA (20 fatal) among the first million patient prescriptions in the United States.<sup>15</sup> In 1999, in a case series of 49 patients with MALA reported from France, 22 patients (45%) died.<sup>2</sup> In 2006, a European study reported 1 death among 10 patients with MALA.<sup>16</sup>

Studies of MALA in ICU patients have also been published — for example, a retrospective case series of 30 patients<sup>1</sup> and another series of 42 patients (13 with voluntary metformin intoxication and 29 with an incidental overdose of metformin).<sup>3</sup> Whether patients with type 2 diabetes have an increased risk of developing lactic acidosis with metformin use remains uncertain. To our knowledge there have been no studies of MALA in Australian ICUs. Our study was designed to evaluate the incidence of MALA in single-centre Australian ICU, and the profile and outcomes of patients admitted to the ICU with this diagnosis.

## Methods

Our study included patients admitted over a 5-year period (January 2003 to December 2007) to a 14-bed tertiary care adult ICU that has a casemix of surgical and medical patients. We did manual searches of ICU discharge summaries, reviewing case notes and cross-referencing with the ICU electronic database, to identify and characterise patients with an ICU discharge diagnosis of MALA. Patients were defined as having MALA if: (i) they had lactic acidosis (plasma lactate level > 2.0 mmol/L, acidaemia (pH < 7.30) and plasma bicarbonate level < 20 mmol/L; (ii) they had been prescribed metformin therapy before ICU admission; and (iii) other causes of lactic acidosis had been excluded by the treating clinician.

Patient data, abstracted into predefined forms, included demographic data, metformin prescription, presenting symptoms, documented premorbid conditions likely to be associated with MALA (hypertension, hyperlipidaemia, congestive cardiac failure, ischaemic heart disease, chronic renal failure), APACHE (Acute Physiology and Chronic Health Evaluation) III score,<sup>17</sup> serial biochemical parameters (arterial blood gas analysis, lactate, urea, creatinine, liver function tests) and ICU therapies (vasoactive medication, mechanical ventilation, dialysis requirement).

Acute renal failure was defined according to the RIFLE (Risk–Injury–Failure–Loss–Endstage renal disease) classification:

- Risk of renal dysfunction (rise of serum creatinine to 1.5 times the baseline level, or urine output < 0.5 mL/kg/hour for 6 hours);
- Injury to the kidney (rise of plasma creatinine to 2 times the baseline level, or urine output < 0.5 mL/kg/hour for 12 hours);
- Failure of kidney function (rise of serum creatinine to 3 times the baseline level, or urine output < 0.3 mL/kg/hour for 24 hours);
- Loss of kidney function (for > 4 weeks); and
- End-stage kidney disease (loss of kidney function for > 3 months).<sup>18</sup>

We used the change in serum creatinine level and urine output to classify patients according to the RIFLE criteria. Outcomes evaluated included ICU and hospital length of stay, duration of invasive mechanical ventilation, and ICU and hospital mortality.

## Statistical analysis

Data were expressed as mean (SD). Differences between continuous and categorical variables were analysed by the *t*-test and Fisher's exact test, respectively.<sup>19</sup> Because of the small sample size (*n* = 17), exact logistic regression<sup>20</sup> was used to model individual variables predictive of hospital mortality outcome expressed as odds ratios (ORs). No multivariable regression was undertaken. Statistical significance was ascribed at *P* ≤ 0.05. Stata version 11 statistical software was used (StataCorp, College Station, Tex, USA).

## Ethics approval

We sought approval from the hospital ethics committee, but due to the retrospective and non-interventional nature of our study, ethics approval was waived.

## Results

Seventeen patients (10 men and 7 women), of mean age 65 (SD, 9.9) years, were diagnosed as having MALA during the 5-year study period, giving an incidence of 6 per 1000 ICU admissions. Two patients' case notes could not be retrieved for further review and the diagnosis of MALA could not be confirmed. The remaining 15 patients had more than one documented comorbidity (Table 1). None of the patients presented with deliberate metformin overdose. The mean dose of metformin that patients were taking at the time of presentation was 1670 (SD, 887) mg/day. Key biochemical variables at baseline, 24 hours and 48 hours are summarised in Table 2. All patients had acidosis at presentation (mean pH 6.92 [SD, 0.26]), with elevated

**Table 1. Demographics and patient characteristics on admission, and association with mortality outcome\***

Variable	Total	Survivors (n = 12)	Non-survivors (n = 5)	P
Age in years	65 (9.9)	65.1 (8.5)	64.8 (14.0)	0.96
Sex (male/female ratio)	10/7	5/7	5/0	0.04
APACHE III score	106.4 (42.9)	94.4 (41.3)	142.3 (26.0)	0.025
Glucose (mmol/L)	11.4 (7.7)	10.8 (8.2)	12.9 (7.0)	0.63
pH	6.92 (0.26)	7.02 (0.23)	6.68 (0.13)	0.002
Bicarbonate (mmol/L)	7.5 (4.8)	8.2 (5.2)	5.9 (3.5)	0.39
Creatinine ( $\mu\text{mol/L}$ )	585 (305)	553 (256)	662 (425)	0.52
(Range; interquartile range)	(106–1070; 490)	(106–966; 442)	(149–1070; 692)	
Lactate (mmol/L)	9.6 (4.1)	8.9 (4.7)	11.4 (1.8)	0.26
Anion gap (mmol/L) <sup>†</sup>	34 (10)	33 (9.5)	38 (13)	0.39
International normalised ratio	2.2 (2.7)	1.6 (1.1)	3.7 (4.7)	0.15
Metformin (mg/day)	1670 (887)	513 (829)	2300 (1131)	0.29
Hypotension (Y/N) <sup>‡</sup>	14/3	9/3	5/0	0.52
Vasopressor (Y/N)	13/4	8/4	5/0	0.26
Invasive ventilation (Y/N)	13/4	9/3	4/1	1.00
Acute renal failure (Y/N) <sup>§</sup>	15/2	11/1	4/1	0.52
Chronic renal failure (Y/N) <sup>¶</sup>	3/13	3/8	0/2	1.00
Hypertension (Y/N) <sup>¶</sup>	4/3	11/1	3/2	0.19
Hyperlipidaemia (Y/N) <sup>¶</sup>	9/8	6/6	3/2	0.99
Ischaemic heart disease (Y/N) <sup>¶</sup>	7/10	5/7	2/3	0.99
Congestive cardiac failure (Y/N) <sup>¶</sup>	2/15	2/10	0/5	0.99
Gastrointestinal symptoms (Y/N)	17/0	12/0	5/0	(undefined)

APACHE = Acute Physiology and Chronic Health Evaluation. \* Figures are mean (SD), except where otherwise specified. † The anion gap is calculated by subtracting the serum concentrations of chloride and bicarbonate (anions) from the concentrations of sodium plus potassium (cations):  $([\text{Na}^+] + [\text{K}^+]) - ([\text{Cl}^-] + [\text{HCO}_3^-])$  (reference range, 8–16 mmol/L). ‡ Defined as systolic blood pressure < 90 mmHg. § Defined by RIFLE (Risk–Injury–Failure–Loss–Endstage renal disease) criteria: creatinine > 150  $\mu\text{mol/L}$  from baseline. ¶ Documented comorbidities.

lactate (mean 9.6 [SD, 4.1] mmol/L) and creatinine (mean 585 [SD, 305]  $\mu\text{mol/L}$ ) levels.

Fourteen patients presented with hypotension and 13 patients required vasopressor agents on admission. Invasive mechanical ventilation was required in 13 patients for a mean of 23.4 (SD, 32.3) hours (range, 0–115.5 hours; interquartile range, 28.5 hours). The mean duration of ventilation was similar in survivors (27.9 [SD, 35.8] hours) and non-survivors (12.7 [SD, 21.1] hours) ( $P=0.39$ ). Two patients had a laparotomy for suspected gut ischaemia, but both investigations were negative.

Based on the RIFLE classification definitions, 13 patients had kidney failure (creatinine level >3 times the baseline level) and two had kidney injury (creatinine level > 2 times the baseline level). Eleven patients received acute renal replacement therapy with sustained low-efficiency daily dialysis (SLEDD), but no patient required dialysis after discharge from the ICU. The mean length of stay in the ICU was 62.8 (SD, 53.5) hours and the mean hospital stay was 11.7 (SD, 3.2) days. Five patients died in the ICU but none died between ICU discharge and hospital discharge. Three variables were

univariately predictive of death in hospital by exact logistic regression: APACHE III score (OR, 1.05 [95% CI, 1.00–1.14];  $P=0.05$ ); arterial pH on admission (OR, 0.01 [95% CI, 0.00–0.89];  $P=0.05$ ); and male sex (OR, 7.32 [95% CI: upper limit not defined, as all who died were male];  $P=0.04$ ).

**Table 2. Trends in biochemical parameters over the first 48 hours with supportive treatment\***

Variable	Admission	24 hours	48 hours
Creatinine ( $\mu\text{mol/L}$ )	585 (305) (IQR, 158)	322 (192) (IQR, 76)	246 (90) (IQR, 118)
Lactate (mmol/L)	9.6 (4.1)	3.2 (2.0)	1.7 (1.0)
Anion gap (mmol/L) <sup>†</sup>	34 (10)	23 (10)	20 (9)
pH	6.90 (0.2)	7.32 (0.1)	7.31 (0.2)
Bicarbonate (mmol/L)	7.5 (4.8)	21.6 (6.0)	20.0 (5.0)
Base excess <sup>‡</sup>	–19.7 (8.5)	–6.0 (6.1)	–2.3 (2.7)

IQR = interquartile range. \* Figures are mean (SD). † Anion gap =  $([\text{Na}^+] + [\text{K}^+]) - ([\text{Cl}^-] + [\text{HCO}_3^-])$  (reference range, 8–16 mmol/L) (for more detail see Table 1). ‡ Reference range for base excess:  $\pm 2$ .

## Discussion

Metformin has been used for more than 40 years for treatment of type 2 diabetes mellitus. The UK Prospective Diabetes Study Group has provided evidence that metformin reduces the risk of morbidity and mortality.<sup>8</sup> In a 2008 meta-analysis, Salpeter and colleagues demonstrated that metformin treatment in people at risk of diabetes resulted in modest reductions in weight and improvements in lipid profile and insulin resistance, and reduced new onset of diabetes by 40%.<sup>21</sup> Metformin use has been progressively increasing. In an Australian study, Kamber and colleagues demonstrated a steady increase in metformin prescriptions over a 5-year period (1996–2001), from 33.3% to 55.1% in their study cohort.<sup>7</sup> The authors also showed that the proportion of patients with estimated glomerular filtration rate <60 mL/min who were prescribed metformin increased from 18.4% to 34.4% over the same 5-year period.<sup>7</sup> Given this background, it is important to assess whether metformin treatment predisposes to the development of MALA, and if so, what factors favour its occurrence and which factors contribute to mortality.

Metformin (1,1-dimethylbiguanide) is structurally similar to phenformin, but because it lacks the large phenyl ethyl side chain of phenformin, it is less hydrophobic and more lipophilic. Metformin is extensively eliminated by the kidneys through active tubular secretion, and the renal clearances of metformin and creatinine are linearly correlated. The mechanism by which metformin causes acidosis is not well described, but is postulated to be related to the suppression of gluconeogenesis.<sup>22</sup> Metformin reduces the activity of pyruvate dehydrogenase and the transport of mitochondrial reducing agents, thus enhancing anaerobic metabolism, which in turn results in increased metabolism of pyruvate to lactate, increasing the net lactic acid production. This shift to anaerobic metabolism is not related to lack of oxygen or to insulin or the increased production of the precursors of the tricarboxylic acid cycle.<sup>23,24</sup>

Our patients demonstrated, not surprisingly, metabolic acidosis (mean pH, 6.92 [SD, 0.26]) and a high anion gap (mean, 34 [SD, 10]), with a mean lactate level of 9.6 (SD, 4.1) mmol/L. In the study by Peters et al (a composite cohort of “concurrent” metformin medication and deliberate overdose), mean pH and lactate levels were 7.18 (SD, 0.19) mmol/L and 9.9 (SD, 4.1) mmol/L, respectively.<sup>1</sup> For 13 patients with “intentional overdose”, Seidowsky and colleagues recorded mean pH and lactate levels of 7.34 (SD, 0.07) and 6 (SD, 7) mmol/L, respectively. However, in a sub-cohort of 29 patients with “circulatory or respiratory failure with multiorgan dysfunction (*incidental* overdose group) ... [our emphasis]”, the acid–base derangements were more severe: mean pH 6.94 (SD, 0.19); mean lactate level 14.6 (SD, 6.5) mmol/L; and mean anion gap 38 (SD, 8).<sup>3</sup> The lactate

levels (but not the pH or anion gap) of this latter group were significantly different from those recorded in our study (mean difference in lactate levels, 5 mmol/L (95% CI, 1.8–8.2 mmol/L;  $P=0.003$ ). Using the Stewart approach<sup>25</sup> to base-excess component evaluation, the major proportion of the base excess was contributed by lactate (9.6 mmol/L), a smaller proportion by strong ions (3.4 mmol/L), and the remainder by other unmeasured anions.

The incidence of MALA in our ICU was 6/1000 admissions, lower than the previously reported prevalence rates of 10/1000<sup>1</sup> and 12/1000<sup>3</sup> from published French studies. The differences in incidence may be explainable by varying definitional thresholds of lactate as well as the inclusion of patients with coincident causes of high lactate levels. In our study, 15 patients had a blood lactate level >5 mmol/L and only two had levels <5 mmol/L (3.1 and 3.9 mmol/L), but both of these patients were admitted to the ICU for profound hypotension and dialysis requirement. In our study, obvious causes of lactic acidosis were excluded by the treating clinician and a subsequent discharge diagnosis of MALA was made. Other studies have included all patients with lactataemia on prescription of metformin,<sup>1–3</sup> with no exclusion of patients with “obvious” causes of elevated lactate levels (tissue hypoperfusion, acute lung injury or cardiac arrest) or voluntary or incidental overdose.<sup>3</sup>

In our study, the pre-morbid dose of metformin and plasma lactate levels on admission were not predictors of outcome. Neither plasma lactate levels on admission nor daily dose of metformin were significantly associated with mortality ( $P=0.26$  and  $0.29$ , respectively) although the point estimate ORs were adverse (1.17 and 1.001, respectively). Other studies have similarly found no relationship between metformin levels and outcome parameters, and survival has been reported in patients with lactate levels as high as 35 mmol/L or more.<sup>1–4</sup>

Several risk factors predisposing to MALA have been proposed. These include renal impairment (plasma creatinine levels  $\geq 1.5$  mg/dL [ $132 \mu\text{mol/L}$ ] for men and  $\geq 1.4$  mg/dL [ $124 \mu\text{mol/L}$ ] for women); severe dehydration; cardiac or respiratory insufficiency; and severe infection and liver disease.<sup>12,22,26</sup> MALA occurs in a previously treated patient with type 2 diabetes when the risk factors or contraindications to the drug have been overlooked. More than two-thirds of our patients had one or more documented risk factor.

In our series, all patients presented with gastrointestinal symptoms. This may have resulted in dehydration and contributed to the development of acute renal failure. The presence of lactic acidosis during metformin therapy is normally attributed to a high plasma lactate concentration caused by renal failure or the presence of other comorbid conditions. Renal dysfunction, a feature in 74%<sup>3</sup> and 80%<sup>1</sup> of patients with MALA in other series, was also evident in 15 out of 17 patients, with 11 patients requiring short-term

renal replacement therapy. In the French study by Seidowsky et al, 74% of patients required dialysis, but the mortality rate in patients with MALA was not altered by haemodialysis.<sup>3</sup> Peters and colleagues demonstrated a trend of higher MALA severity scores (Simplified Acute Physiology Score [SAPS] II) among MALA patients who required dialysis ( $P=0.04$ ).<sup>1</sup>

Metformin can theoretically be extracted from blood by haemodialysis. Although several modalities of dialysis have been described for MALA, including SLEDD and peritoneal dialysis,<sup>27-31</sup> the efficacy of different dialysis modes has not been determined. Treatment is largely supportive and includes elimination of the offending medication, correcting acid-base disturbances and treating and supporting organ failure.

The mortality rate of 5/17 (29%) in our Australian study compares favourably with the 30% and 33% reported in the two French studies that have described MALA in ICU patients.<sup>1,3</sup> The mortality rate has varied in non-ICU cohorts from 1/10 (10%) in a series of 10 patients<sup>16</sup> to 22/49 (45%) in an earlier series.<sup>2</sup> The study of Seidowsky et al suggested a prothrombin activity of <50% as an independent predictive factor of mortality (relative risk, 59.8 [95% CI, 6.3–568];  $P<0.001$ ), although the upper limit of the 95% CI suggests parameter instability.<sup>3</sup> This relationship was not evident in our study ( $P=0.15$ ).

## Conclusions

Metformin-associated lactic acidosis is a not uncommon cause of admission to the ICU, and is associated with significant morbidity and mortality. Gastrointestinal symptoms are commonly present. In our Australian study, arterial pH, admission severity of illness (APACHE III) score and male sex were all predictors of hospital outcome.

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