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Metformin associated lactic acidosis (MALA): clinical profiling and management

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Abstract Metformin (MF) accumulation during acute kidney injury is associated with high anion gap lactic acidosis type B (MF-associated lactic acidosis, MALA), a serious medical condition leading to high mortality. Despite dose adjustment for renal failure, diabetic patients with chronic kidney disease (CKD) stage III–IV are at risk for rapid decline in renal function by whatever reason, so that MF toxicity might arise if the drug is not timely withdrawn. Sixteen consecutive patients were admitted to our Hospital's Emergency Department with clinical findings consistent with MALA. Fifteen had prior history of CKD, 60 % of them with GFR between 30 and 60 ml/min. Of these, 5 required mechanical ventilation and cardiovascular support; 3 promptly recovered renal function after rehydration, whereas 10 (62 %) required continuous venovenous renal replacement treatment. SOFA and SAPS II scores were significantly related to the degree of lactic acidosis. In addition, lactate levels were relevant to therapeutic choices, since they were higher in dialyzed patients than in those on conservative treatment (11.92 mmol/l vs 5.7 mmol/l, $p = 0.03$). The overall death rate has been 31 %, with poorer prognosis for worse acidemia, as serum pH was significantly lower in non-survivors (pH 6.96 vs 7.16, $p > 0.04$). Our own data and a review of the literature suggest that aged, hemodynamically frail patients, with several comorbidities and CKD, are at greater risk of MALA, despite MF dosage adjustment. Moreover, renal replacement therapy rather than simple acidosis correction by administration of alkali seems the treatment of choice, based on eventual renal recovery and overall outcome.

Keywords Metformin · Type 2 diabetes · Lactic acidosis · Acute renal failure · Bicarbonate · Hemodialysis

Introduction

Metformin (dimethylbiguanide, MF) is a long-known oral hypoglycemic agent, increasingly used in recent years as a first-line therapy in Diabetes Mellitus (DM). Long-term treatment with MF results in better day-time glucose profile regulation with less risk of hypoglycemia, better adipose mass control, lower rates of cardiovascular disease and overall mortality [1–6]. MF decreases hepatic gluconeogenesis from lactate and enhances peripheral glucose uptake. Absorption occurs in the small intestine. It has negligible plasma protein binding and a large distribution volume (from 63 to 276 L). It undergoes virtually no hepatic metabolism and it is excreted by the kidney [7–9]. Consequently, it may accumulate during acute or chronic kidney injury (AKI/CKD), resulting in high anion gap lactic acidosis type B (MF-associated lactic acidosis, MALA), a rare but severe metabolic adverse effect (43 cases/100,000 patients/years) [10–14].

The mechanism by which MF increases blood lactate concentration is complex, with mitochondrial inhibition of the respiratory chain complex as a likely major player [7, 8]. MF promotes (i) the conversion of glucose to lactate by the intestinal mucosa, and (ii) blocks mitochondrial

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oxidative metabolism, decreasing hepatic gluconeogenesis from lactate, pyruvate and alanine; this, in turn, results in anaerobic glycolysis and lactate accumulation at concentrations relevant to clinical intoxication [7, 15, 16]. At variance with other biguanides, MF does not inhibit lactate oxidation and does not enhance lactate release from muscle. This may attenuate the risk of lactic acidosis upon MF accumulation due to reduced renal clearance [17].

MALA seems to occur in certain settings only. This has led to the development of exclusion criteria for its use in the management of DM, such as renal insufficiency, cardiopulmonary insufficiency, liver disease, sepsis, alcohol abuse, administration of i.v. radiographic contrast agents, and a previous history of lactic acidosis [5, 18–22].

In renal failure, strict biochemical parameters monitoring and adherence to dose adjustment are recommended by current treatment guidelines. As far as renal dysfunction is concerned, MF may be initiated or continued with eGFR <60 mL/min/1.73 m^2, but renal function should be assessed at regular intervals (3–6 months). Doses should be reduced by 50 % in subjects with eGFR <45 mL/min/1.73 m^2. MF should be stopped whenever eGFR drops below 30 mL/min/1.73 m^2 [23–31].

This assumption is valid for steadily impaired renal function but, as a result of the combination of chronic kidney disease, diabetes and other traditional risk factors (elderly pts., inadequate fluid intake, marked volume losses obligated by the renal excretion of non-reabsorbable solutes in CKD), certain individuals are at particularly high risk of hemodynamic changes leading to sudden drops of GFR [32–34]. Therefore, it should be envisioned that in CKD stage 3–4 there is a risk for rapid, further decline in renal function and, consequently, MF may suddenly accumulate, leading to metabolic/lactic acidosis. In order to better clarify the clinical picture and outcomes of MALA, we retrospectively reviewed the charts of 16 consecutive patients admitted to our Hospital's Emergency Dept. with clinical findings consistent with the diagnosis of MALA. Our experience is herein summarized in light of the vast literature that is rapidly accumulating as a result of the revival and widespread use of this old oral antidiabetic agent.

Patients and methods

All patients with MALA admitted to our Center over a 5-year period (from January 2009 to June 2014) were included in the present study, whenever matching the following inclusion criteria: history of type 2 DM in MF treatment, blood pH <7.3, serum HCO$_3^-$ <22 mEq/l, serum lactate >5 mmol/l. Survivors gave an informed consent to data collection as requested by the Institution's Ethics Committee. Exclusion criteria were: self-

Table 1 Clinical/laboratory criteria for patients' selection

Inclusion criteria
pH <7.3
HCO$_3^-$ <22 mEq/l
Lactate >5 mmol/l
Exclusion criteria
Self- administered overdose
Lactic acidosis type A
Diabetic ketoacidosis
Tumor lisys
Hepatic insufficiency
Respiratory insufficiency
Cardiac insufficiency

administered overdose, lactic acidosis type A, diabetic ketoacidosis, tumor lysis syndrome, history of severe hepatic, respiratory and cardiac insufficiency (Table 1).

The study variables analyzed were: (1) demographic-anamnestic data (age, sex, pre-existing chronic kidney disease, cause of acute kidney injury (AKI), MF dose, other potentially nephrotoxic therapies); (2) laboratory data [basal serum creatinine and eGFR, biochemistry including serum glucose levels, anion gap and arterial blood gas analyses (ABG) at admission and discharge]; (3) biological parameters at admission (blood pressure, heart rate, body temperature, urine output, Glasgow Coma Scale); (4) illness severity scores of patients presenting to the Emergency Dept., including Sequential Organ Failure Assessment (SOFA) and Simplified Acute Physiology Score II (SAPS II), with the probability of death calculated for each patient based on these scores; (5) therapies; (6) outcomes.

Data analysis was performed using the PASW Statisitics 17 software for Windows. Univariate analysis was used to describe the sample characteristics. Simple linear regression analysis was used to determine strength and direction of the relationship between each dependent variable (SOFA score, SAPS II, baseline GFR) and each explanatory variable, all of which pre-HD (pCO$_2$, lactates, pH, HCO$_3^-$). Scatterplot graphs were created and Pearson's correlation coefficients with the associated test of statistical significance were computed. Adjusted R square was used to calculate the proportion of variation in the dependent variable accounted by the explanatory variables. Multiple linear regression analysis was used to investigate the relationship between a set of predictor variables and a single dependent variable.

Results

We identified 16 consecutive type 2 diabetic patients with diagnosis of MALA (Tables 2, 3) within 24 h of admission to our Unit or the Emergency Dept. All patients presented

Table 2 Demographic–anamnestic variables

	No. of patients: 16	Range
Age (years)	73.13 ± 11.55	54–90
Sex (m/f) %	56.3/43.8	
eGFR (MDRD equation)		
>60 ml/min	1 (6.3 %)	
30–60 ml/min	9 (56.3 %)	
<30 ml/min	3 (18.7 %)	
Unknown	3 (18.7 %)	
Metformin daily dose (g)	2.5 (0.8–3)	
Other therapies potentially affecting renal function (%)		
Diuretics	56	
ACE-inhibitors	75	
NSAIDs	6.3	
ASA	6.3	
Hospitalization (days)	14.5 ± 7.64	5–30

Data are mean ± SD

Table 3 Clinical characteristics

		Range
Serum Cr, baseline (mg/dl)	1.61 ± 0.59	0.8–3.1
Serum glucose (mg/dl)	186 ± 134	50–643
GFR baseline (ml/min)	42.57 ± 15.13	19–78
sCr (admission) (mg/dl)	8.05 ± 3.65	2.5–13.7
GFR (admission) (ml/min)	8.30 ± 6.26	4–26.6
BUN (mg/dl)	98.50 ± 34.47	45–169
K^+ (mEq/l)	6.57 ± 1.14	4.2–8.2
pH	7.1 ± 0.19	6.80–7.36
HCO_3^- (mEq/L)	10.23 ± 4.62	3–18.6
Lactate (mmol/l)	9.58 ± 4.38	5–>15
SOFA score	8.81 ± 3.41	3–16
SAPS II score	64.81 ± 16.96	41–100
Estimated mortality (SAPS II)	69.85 ± 21.69	26.6–98.5

with AKI following a prolonged episode of dehydration, with variable SOFA and SAPS II scores.

Prior to admission, the patients' renal functional status—retrospectively assessed—ranged from normal kidney function to K/DOQI stage 5 chronic kidney disease (Table 4). Dosage of MF was properly adjusted except for 5 patients, which were otherwise on a stable medication regimen until the occurrence of a superimposed AKI and subsequent development of MALA. The clinical picture was generally more serious as a function of worsening renal dysfunction. Among all subjects with prior renal impairment (15 pts.), 60 % of them with GFR between 30 and 60 ml/min (Table 4). Acidosis in this group was more severe, with an average pH <7.0, HCO_3^- <10 mEq/l and lactate >10 mmol/l.

Table 4 No. of patients based on Glomerular filtration rate—K/DOQI stage

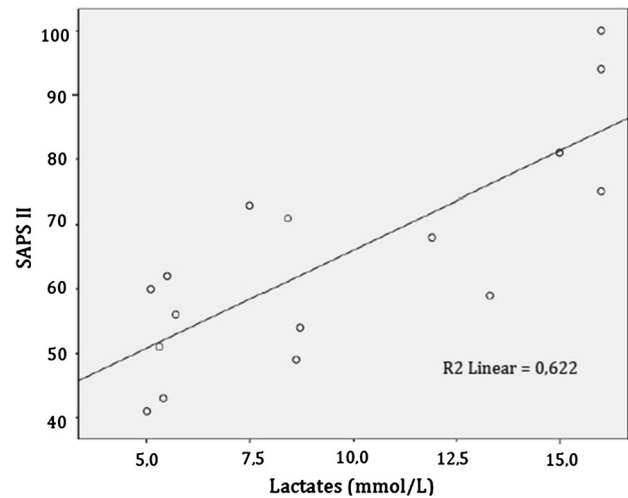| No. of patients	
GFR <30: stop metformin (stages 4–5)	3
GFR <45 and ≥30: 50 % dose (stage 3B)	4
GFR <60 and ≥45 (stage 3A)	5
GFR ≥60 (stages 1–2)	1
GFR unknown	3
Total	16

Fig. 1 Linear regression analysis of the relationship between Simplified Acute Physiology Score. II (SAPS II), and pre-HD lactates as an explanatory variable. R square 0.622; adjusted R square 0.595; SE of the estimate 10.794

SOFA and SAPS II scores, used to assess severity of comorbidities, were significantly influenced by all parameters linked to MALA (pH, HCO_3^-, lactates: $p < 0.01$; as an example, SAPS II vs lactates is shown in Fig. 1). Patients were initially treated with iv fluid infusions, including administration of $NaHCO_3$. Five patients required mechanical ventilation and cardiovascular support. Three promptly recovered renal function after rehydration, whereas 13 required renal replacement therapy, 77 % of whom treated with continuous veno-venous techniques. Serum lactate was an important benchmark for therapeutic choices: mean lactate concentration was significantly higher in dialyzed patients compared with those in conservative treatment (lactate 11.9 vs 5.7 mmol/l, $p = 0.03$, Table 5).

The overall death rate was 31 % (n = 5 patients, Table 6). There were no significant differences in demographic, biochemical and physical data for the group of patient who survived compared to those who died. The poor prognosis was primarily associated with the degree of acidemia, as shown by the threshold ABG results

Table 5 Acidosis pattern and illness severity scores vs renal supportive treatment

	Treatment		
	Conservative (19 %)	HD (81 %)	p value
pH	7.31 ± 0.1	7.06 ± 0.2	<0.05
HCO_3^- (mEq/l)	16.07 ± 2.2	8.87 ± 3.9	<0.05
Lactate (mmol/l)	5.3 ± 0.3	10.34 ± 4.3	<0.05
SOFA score	4 ± 1.7	7.7 ± 3.1	NS
SAPS II score	47.67 ± 11.6	63.31 ± 16.0	NS

Table 6 Clinical parameters vs outcome

Mortality

Overall mortality: 31 % (5 patients)

Mortality for pH <7.2 % (3/5 patients)

Mortality for lactate >10 mmol/l: 50 % (3/6 patients)

Mortality for HCO_3^- <10 mEq/l: 33 % (3/9 patients)

	Survivors (n = 11)	Non-survivors (n = 5)
Age (years)	71.64 ± 11.6	76.6 ± 11.9
GFR (baseline)	39.51 ± 17.2	49.48 ± 5.7
GFR (admission)	8.17 ± 6.7	8.57 ± 5.9
BUN	100.36 ± 40.5	94.2 ± 17.8
pH	7.16 ± 0.2	6.96 ± 0.2 (p < 0.04)
HCO_3^-	11.24 ± 4.4	8 ± 3.8
Lactate	8.6 ± 4.4	11.76 ± 3.8
SOFA	6.73 ± 3.7	7.8 ± 2.1
SAPS II	57.1 ± 16.5	67.6 ± 10.4
Vasoactive support	2 patients	4 patients
Mechanical ventilation	3 patients	4 patients

correlated with the hard outcome: n = 3 deaths out of 5 patients with pH <7.0, 3 out of 6 with lactate >10 mmol/l, and 3 out of 9 with HCO_3^- <10 mEq/l. The magnitude of decrease in pH was, indeed, significantly greater in non-survivors (pH 6.96 vs 7.16, p < 0.04, Table 6).

Discussion

Lactic acidosis is a recognized adverse effect of MF treatment, with a modest overall incidence of 3–10 per 100,000 person-years [14, 20]. The range of reported incidence varies widely based on the general conditions and/or renal function of diabetic individuals receiving MF treatment. Of course, the possibility that MALA could occur unrecognized in a number of patients must not be discounted. Whenever strict criteria for withdrawal of MF (e.g. a cutoff of eGFR <30 ml/min) are met, the occurrence of MALA decreases below 5 per 100,000 person-years,

which is not different from the rates observed with other oral antidiabetic agents. A series of Cochrane systematic reviews by Salpeter et al. has pooled some 347 studies encompassing 70,490 type 2 diabetic patient-years receiving MF treatment, without noting a single case of MALA. Of these, 43 % of patients were enrolled without evaluating renal function, so that the data should not be considered censored for renal failure [13, 19]. These figures, and the fact that MF levels in individuals with lactic acidosis have often been found normal or only slightly elevated, have led some Investigators to question the strength of this association [13, 35–37]. Moreover, even the relationship between MF serum levels and renal failure is uncertain. Despite the fact that MF is excreted unmodified mostly by the kidney, evidence that the drug accumulates to high levels in patients with acute kidney injury or CKD stages 4–5 is lacking [10, 13, 24, 26, 38]. Even though a review of 223,968 patients employing MF reported a higher hazard ratio for MALA whenever eGFR decreased below 60 mL/min, and even more so below 45 ml/min, the study suffered from several biases, including lack of renal data in 25 % of the patients, younger average age and lactate measurements in the MF group only [24]. Another analysis on the same database yielded a trend in increasing incidence ratio of MALA among individuals with impaired renal function, which was not statistically significant due to rarity of the event [38]. It should also be pointed out that severity of lactic acidosis is not directly proportional to MF serum levels, with some critical patients exhibiting only mild MF accumulation [33]. Other factors are evidently implicated in lactic acidosis, consistent with a number of known causes of the A, B1, B2, and B3 subtypes of this metabolic derangement. On the other hand, severity of lactic acidosis is clearly linked to a worse clinical condition and prognosis, as also shown by our series.

Nevertheless, MALA is a severe condition with poor prognosis in the absence of immediate treatment [30, 31, 39, 40]. Because administration of MF is associated with a lower incidence of cardiovascular events and mortality, several regulatory Agencies and Authorities advocated in recent years a less restrictive use of this agent, provided that dose reduction was granted on the basis of eGFR, according to current guidelines [41–45]. However, this

assumption takes into account mostly subjects with stable renal impairment. In fact, we herein noted once more how renal function may suddenly decline significantly as a consequence of effective circulatory volume or renal hemodynamics in patients with CKD. As a matter of fact, in 100 % of our patients MALA was associated with pre-renal AKI superimposed to an underlying CKD.

The onset of MALA is associated with worsening general health conditions, as evaluated with SOFA and SAPS II scores. Severity of comorbidities is strictly connected to ABGs: our study underlines a significant correlation between illness severity, serum HCO_3^- and lactate levels. Likewise, these changes are also critical for the selection of therapeutic options [46–49].

In our series, intensive management in the Emergency Dept. upon admission usually included intravenous fluid and $NaHCO_3^-$ administration, vital function support (5 pts required mechanical ventilation and cardiovascular support), HD in selected cases, and treatment of underlying conditions [50–52]. A conservative treatment was recommended by our consultant Nephrologists in 19 % of cases (average pH 7.31, HCO_3^- 16.0 mEq/l, lactate 5.3 mmol/l, SOFA score 4, SAPS II 47.67). In these patients, i.v. rehydration therapy led to rapid GFR recovery and parallel reduction of serum lactate levels.

In most critically ill patients (81 %) with severe multiorgan damage and hemodynamic instability (pH 7.06, HCO_3^- 8.87 mEq/l, lactate 10.34 mmol/l, SOFA 7.7, SAPS II 63.31), MALA required management by continuous renal replacement therapy (CRRT, 49). Goals of resuscitation in severe metabolic acidosis include maintenance of CVP >8 mmHg, $ScvO_2$ >70 % and normalization of lactate, while $NaHCO_3$ administration remains controversial [48]. Most current guidelines do not recommend administration of $NaHCO_3$ in patients with lesser degrees of lactic acidosis (i.e., pH >7.1), since prompt correction of acidosis may remove any obstacle to anaerobic glycolysis and hence actually promote lactate accumulation and further intracellular acidification [49, 50]. Intracellular acidosis itself is actually a powerful inhibitor of lactate generation [49]. Moreover, $NaHCO_3$ promotes CO_2 accumulation through dehydration of H_2CO_3 resulting from combination of H^+ and HCO_3^-. In the absence of sufficient CO_2 elimination, $NaHCO_3$ exacerbates intracellular CO_2 influx, paradoxically leading to intracellular acidification. Furthermore, intracellular acidification due to accumulation of CO_2 after $NaHCO_3$ infusion brings about a pH-dependent decrease in levels of $[Ca^{2+}]_i$, a modulator of cardiac contractility. Additional risks of $NaHCO_3$ administration include increased plasma CO_2, hyperosmolality, hypernatremia, volume overload, and pH overcorrection, resulting in metabolic alkalosis [48]. This increases the need for respiratory assistance in

these subjects. Overall, HD is an efficient method of drug removal and acidosis correction, particularly in critically ill patients [51, 52]. In survivors (69 %), gradual improvement in all AB variables has been observed. At the other hand of the spectrum, worsening of acidosis portends a less favourable prognosis. It has been actually shown that late-referral patients, with a higher degree of acidemia at the time of admission, have a worse prognosis compared to earlier identified cases. Based on our series, it seems fair to conclude that aged, hemodynamically frail patients, with several comorbidities and renal impairment from moderate to severe, are at greater risk of MALA, despite dosage adjustment. The most serious the threat, with high lactate and low HCO_3^- levels, the worse was the clinical outcome.

In conclusion, while data in the literature seem to support an "MF to all, all the time" paradigm, our report suggests a more careful approach, particularly among patients with CKD stage 3–4 who may have serious clinical conditions predisposing to AKI. It seems sensible to withdraw MF whenever subjects at risk of abrupt worsening of renal function are identified through frequent monitoring of eGFR and other hemodynamic parameters, switching to other oral antidiabetic agents or insulin whenever unstable clinical conditions are detected. Moreover, early detection of any acid–base imbalance not solely explained by renal failure (i.e., high anion gap acidosis) should prompt the search for elevated serum lactate levels, and raise concerns about routine alkali administration.

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