

# Metformin-associated lactic acidosis: A prognostic and therapeutic study\*

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**Objectives:** Metformin-associated lactic acidosis is a rare and serious complication of biguanide treatment. It usually occurs when a precipitating disease induces an acute renal failure and an incidental overdose. Voluntary intoxication is rare. Bicarbonate hemodialysis (HD) is recommended to decrease metformin levels and correct acidosis but its optimal duration has not been determined. This study was designed to document the characteristics and prognostic factors of intentional and incidental metformin overdose and to determine the optimal duration of HD.

**Design:** Ten years retrospective analysis of patients admitted in intensive care unit for metformin-associated lactic acidosis.

**Setting:** Two intensive care units (50 beds) in a university hospital.

**Measurements and Main Results:** Clinical and biological characteristics, organ failures, and sequential metformin levels during HD were recorded. Forty-two patients were included (13 voluntary intoxications and 29 incidental overdoses); 74% of patients were in acute renal failure and needed HD. No death was observed in intentional overdose patients compared with 48.3% mortality in incidental overdose patients. The factors significantly associated

with mortality were logistic organ dysfunction system score, pH, plasma lactate, and prothrombin activity. By multivariate analysis, a prothrombin activity <50% was the only independent predictive factor of mortality (relative risk: 59.8; confidence limits: 6.3–568;  $p < 0.0001$ ). Sequential measurements of metformin levels during HD were consistent with a bicompartmental elimination pattern. A cumulative HD duration of 15 hours was associated with the return of metformin level to the therapeutic normal range.

**Conclusions:** In our study, the outcome of MALA was uniformly favorable after intentional metformin overdose. The vital prognosis was mainly influenced by the occurrence of multiple organ dysfunctions, the best predictive factor of death being an acute liver dysfunction as assessed by PT activity. Prolonged HD was needed to correct metformin overdose. (Crit Care Med 2009; 37: 2191–2196)

**KEY WORDS:** metformin; lactic acidosis; pharmacokinetics; prognosis; liver dysfunction; prothrombin activity; hemodialysis; intoxication; diabetes

**M**etformin therapy reduces microvascular complications in type 2 diabetic patients and is increasingly used worldwide. The possible occurrence of a severe lactic acidosis is known as one of its adverse effects. In contrast with the huge number of treated patients, metformin-associated lactic acidosis (MALA) is rare, with an estimated incidence of three per 100,000 metformin-treated pa-

tients per year, but is associated with a high mortality rate, averaging 50% (1). In most cases, MALA occurs in a previously treated type 2 diabetic patient when the contraindications of the drug have been overlooked or more often when a concurrent disease induces an acute renal failure leading to metformin accumulation (2–4). In rare cases, MALA is due to a voluntary intoxication and may be observed in nondiabetic healthy children or adults (5). These cases of voluntary acute metformin intoxications have been rarely reported in the literature and their characteristics and prognosis have not been compared with incidental metformin overdose.

Blood purification by hemodialysis (HD) is considered adequate treatment of MALA because it efficiently removes metformin and lactate by diffusion through the dialyzer membrane. Additionally, a bicarbonate-buffered and high-sodium dialyzate improves the metabolic acidosis and increases blood volume, thus enhancing the renal blood flow. These advantages are of special interest in patients

suffering from severe sepsis or diarrhea-induced dehydration (6, 7). Most authors recommend a prolonged duration of HD in these patients, but pharmacokinetic data documenting the removal characteristics in metformin overdose are scarce.

Therefore, we designed this study to document the main characteristics and prognostic factors of patients admitted in the intensive care unit (ICU) for a life-threatening MALA. We sought to compare patients receiving metformin who developed an incidental overdose with patients admitted for an acute voluntary intoxication. The second aim of the study was to determine the optimal duration of HD according to the characteristics of metformin elimination observed during HD procedures.

## PATIENTS AND METHODS

This was a retrospective study that used the database of the two ICUs (50 beds) and of the toxicology laboratory of our university hospital to identify the patients admitted for a MALA from January 1998 to January 2007. The patients' files were identified by an auto-

\*See also p. 2312.

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**Table 1.** Main clinical and biological characteristics of patients at admission in the intensive care unit

Characteristics	n = 42
Age (yrs)	61 ± 15 (16–81)
Male/female, n (%)	19/23 (45/55)
Total LODS score (points)	6 ± 4.1 (0–14)
Probability of mortality based on the LODS score (%)	39 ± 8 (3.2–92)
Arterial pH	7.1 ± 0.23 (6.6–7.44)
Plasma bicarbonate (mmol/L)	10 ± 7 (2–21)
Blood urea (mmol/L)	17.6 ± 15.5 (0.46–83)
Blood creatinine (μmol/L)	386 ± 309 (35–1126)
Plasma lactate (mmol/L)	11 ± 6.9 (2.9–30)
Plasma anion gap (mmol/L)	33 ± 11 (12.3–50)
Plasma metformin level (mg/L)	27 ± 24.5 (3–83)
Prothrombin activity (%)	59 ± 31 (10–109)
Need for vasoactive support, n (%)	21 (50)
Need for mechanical ventilation, n (%)	19 (45)
Acute renal failure, n (%)	31 (74)

LODS, logistic organ dysfunction system.

Data are expressed as mean ± SD (extreme values).

mated and manual search of discharge records in the two ICUs and in laboratory databases. Medical records were studied by one author only (A.S.) and patients' personal data were rendered anonymous before statistical analysis. Given that this was a purely retrospective noninterventional study and according to French law, the local ethics committee waived the need for approval of the study.

The definite diagnosis of MALA was considered when the diagnosis had been stated by the clinicians in charge and when the patient's medical records could document at admission a status of hyperlactatemic metabolic acidosis and metformin accumulation assessed by a plasma level higher than 2 mg/L, either due to voluntary intoxication or incidental overdose.

During the whole study period, plasma metformin concentrations were measured by high-performance liquid chromatography (normal therapeutic range: 0.5–2 mg/L).

The following clinical and biological characteristics were studied in all patients:

1. Clinical characteristics: age; gender; preexisting diabetic disease; baseline chronic treatment; occurrence at admission in the ICU of respiratory failure, gastrointestinal disorders (nausea, vomiting, jaundice), neurologic dysfunction (confusion, coma),

or cardiovascular dysfunction; need for vasoactive drugs, mechanical ventilation, or extrarenal support; duration of ICU and hospital stay; and mortality in ICU.

2. Worst biological values recorded in the first 24-hour period in ICU: arterial blood gases (pH,  $P_{aO_2}$ ,  $P_{aCO_2}$ ,  $HCO_3^-$ ); arterial lactate; blood urea nitrogen and serum creatinine; glycemia, plasma electrolytes (Na, K, Cl, Ca, and P); plasma anion gap; erythrocyte, leukocyte, and platelet counts; activated partial thromboplastin time; and prothrombin (PT) activity. PT activity was expressed in percent of normal level. It corresponds to the Quick coagulation time, measured in seconds, and in this case was compared with the coagulation time of healthy subjects (usual normal range: 10–12 seconds, corresponding to 70% to 120% activity). The logistic organ dysfunction system was used to assess organ dysfunction in all patients. This score has been validated to accurately measure the severity of organ dysfunctions and their sequential changes during the ICU stay. The score identifies six different organ dysfunctions: neurologic, cardiovascular, renal, pulmonary, hematologic, and hepatic. The total score may vary from 0 (all variables normal) to 22 (all variables at worst possible values) and may be used to calculate a predicted mortality (8).

3. Characteristics of the extrarenal support: The decision to treat patients by HD was made by the physicians in charge in the two ICUs. There was no definite written protocol for this specific situation. Continuous hemo(dia)filtration was not used because metformin elimination from blood and correction of severe hyperlactatemic acidosis are best achieved by a diffusion process across the dialyzer membrane. All patients were hemodialyzed *via* a venous femoral or jugular blood access on polysulfone or polyacrylonitrile dialyzers and with a low-temperature (36°C), high-sodium, bicarbonate-buffered dialysate. The ultrafiltration rate and modalities of anticoagulation were adapted by the physicians in charge. During the whole study period, there were minimal changes in these HD settings. Both ICUs have used high-permeability dialyzers and bicarbonate buffer since 1985 and there was no significant difference between the two ICUs in the characteristics of extrarenal support, except for anticoagulation. One ICU used standard heparin and the other low-molecular-weight heparin for prevention of blood line clotting.

**Statistical Analysis.** Data are presented as means ± SD for the entire population and as medians, interquartile range, and extreme values for comparisons between groups. Patients suffering from incidental overdose were com-

pared with patients with intentional overdose, and survivors to nonsurvivors, by the Mann-Whitney *U* test and Fisher's exact test when appropriate. Optimal threshold for numerical parameters were determined by receiver operating characteristics analysis. Explanatory variables of mortality were determined by univariate analysis. Relative risks were computed using logistic regression. Independent risk factors of mortality were assessed by a stepwise logistic regression. Sensitivity, specificity, and relative risk were calculated by standard formulae. Statistical significance was defined as  $p < 0.05$ .

## RESULTS

### Main Characteristics of the Patients.

Of the patients, 42 were included in the study, representing 0.12% of the 33,320 patients admitted in the same period of time in the two ICUs. Their main clinical and biological characteristics are shown in Table 1. All patients were chronically treated with metformin for a type 2 diabetes mellitus. Overall at admission, 50% of the patients were in circulatory shock and required a vasoactive support, 45% needed mechanical ventilation, 15% had a severe neurologic dysfunction, and 74% were in acute renal failure. Thirteen patients were admitted for a suicide attempt with metformin voluntary intoxication and constituted the intentional overdose group (group I). In the 29 other patients, the reasons for admission to ICU were always a circulatory or a respiratory failure with multiorgan dysfunction (incidental overdose group: group II). Main results of the comparison between both groups are shown in Table 2. In the entire population, a significant correlation was found between metformin levels and pH ( $r = .764$ ;  $p < 0.0001$ ; Fig. 1A).

**Prognostic Factors.** At admission, the mean probability of mortality based on the logistic organ dysfunction system score was 39%. Fourteen of the 42 patients (33%) died in the hospital. The overall mortality rate in group II was 48.3%, whereas 100% of patients in group I recovered without sequelae. The main results of univariate comparison between survivors and nonsurvivors are shown in Table 3. By univariate analysis, significant differences were found between survivors and nonsurvivors as for age ( $p = 0.016$ ), arterial pH ( $p = 0.005$ ), arterial lactate level ( $p = 0.01$ ), PT activity ( $p < 0.0001$ ), need for mechanical ventilation ( $p = 0.0007$ ), and need for vasoactive support ( $p = 0.003$ ). There was no relevant difference in mean metformin levels between survivors and non-

