Case report

pH 6.68—surviving severe metformin intoxication*

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Metformin, a widely used anti-diabetic agent of the biguanide family, although generally safe,1,2,3,4 holds the risk of developing a potentially lethal acidosis.5,6 The association between lactic acidosis and metformin is well-established but rarely seen in patients taking this medication.7 Its elimination relies solely on kidneys’ excretion,8 so its accumulation is feasible in just two circumstances: renal failure (RF) and acute overdosage.

At normal dosage, a toxic accumulation of drug requires time after the development of RF, due to metformin high clearance. About 90% of the drug is eliminated by glomerular filtration and tubular secretion (serum half-life of 1.5–5 h). Moreover, RF is itself associated with acidosis as it impairs kidneys’ ability to excrete protons. Acute intoxication on the other hand is a viable option in those cases where renal function is normal and can correlate with a psychiatric disorder.

The mechanism thought to be responsible for lactic acidosis is suppression of gluconeogenesis forming lactate, pyruvate, glycerol and amino acids leading to lactate accumulation,9 a risk that is increased by either chronic or acute RF (ARF). Usually hyperlactatemia is the most common finding leaving lactic acidosis for the most severe intoxications.

Case report

A 47-year-old, apparently previously fit, non-insulin-dependent diabetic male was brought to the Emergency Department for hypoglycemia, agitation and hyperventilation. Ambulance crew found blood glucose level at 1.33 mmol/l (24 mg/dl) and administered 20 ml of 33% glucose solution followed by other 250 ml at 5%. At the arrival in the Emergency Room, the patient was confused and agitated with no signs of respiratory distress or shock.

Arterial blood gases (ABG) and laboratory tests are summarized in Table 1 and show a clear clinical presentation of acute metabolic acidosis of unknown etiology with respiratory compensation, as a result 200 ml of sodium bicarbonate (8.4%) were given intravenously to correct pH and 500 ml of dextrose (5%) to avoid hypoglicemia.

Electrocardiogram showed sinus tachycardia, right bundle branch block, repolarization alterations. Abdominal ultrasound examination showed no abnormalities.
A second ABG sample shows an improvement in pH to 7.08 and plasma bicarbonate to 7.7 mmol/l as a response to medical therapy. However, urine output was negligible even after further fluid administration, urea and creatinine levels were severely elevated, so the patient was transferred to the Department of Nephrology of a nearby hospital due to the need of dialysis to treat the underlying ARF.

As soon as dialytic procedure was started, the patient became more and more agitated (heart rate 120 b.p.m.; blood pressure 105/58 mmHg). ABG demonstrated worsening of acidosis (pH 6.8), so that the Intensive Care Unit (ICU) Emergency Medical Team was activated.

At the arrival of ICU personnel, the patient was very dyspneic even if saturation of peripheral oxygen (SpO2) was 100%, but the further alteration of conscience status called for intravenous sedation, orotracheal intubation with manual bag-valve ventilation [fraction of inspired oxygen (FiO2) 1.0] and referral to ICU for intensive support.

At the arrival in ICU, the subject was sedated with benzodiazepines continuos infusion, mechanically ventilated, SpO2 99%, blood pressure 80/40 mmHg and central venous pressure 15 mmHg. The first ABG after arrival in ICU showed an even more compromised metabolic picture with a pH of 6.68, PaCO2 15.5 mmHg and plasma bicarbonate 1.8 mmol/l. ABG, procedures undertaken in ICU and laboratory findings at different time intervals are summarized in Table 1.

Infusion of sodium bicarbonate (8.4%) was immediately started, but after the first 400 ml for over 1 h no significant change in pH was achieved. Serum lactate was elevated consistently with the clinical picture of metabolic acidosis, hence continuous veno-venous hemofiltration (CVVH) was implemented alongside medical therapy to lower its level as urine output remained negligible. During the procedure, an episode of severe bradycardia not responsive to atropine or epinephrine lead to cardiac arrest. After successful resuscitation, a vaso-active therapy with norepinephrine continuous infusion at 0.02 mg/kg/min was begun: blood pressure reached 90/50 mmHg on average.

Metformin intoxication was taken into account as a possible cause of lactic acidosis with an underlying ARF, as the patient was taking the drug on a daily basis for diabetes. San Matteo Hospital’s (Pavia, Italy) Poison Control Center was contacted to dose plasma metformin. In fact its concentration was 10 times higher than normal therapeutic levels, a condition that leads to lactic acidosis, for the

<table>
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<th>4</th>
<th>6</th>
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<td>6.85</td>
<td>7.09</td>
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</table>

Relevant events, ABG samples and laboratory findings during the first 47 h after hospital admission. Time is expressed in h after emergency room (ER) admission and Time 2 corresponds to ICU admission. HCO3⁻, infusion of sodium bicarbonate; CPR, cardio-pulmonary resuscitation; NE, infusion of norepinephrine; Urine, urine output; AG, anion gap; Glu, glucose; Crea, creatinine; Na, sodium; K, potassium; Lac, lactate; Met, metformin; ALT, alanine aminotransferase; BE, base excess.
continuous cellular production and release of lactic acid, above liver-clearing capacity. After cardiac arrest, CVVH was changed to continuous veno-venous hemodialysis (CVVHD) in order to ultimately accelerate lactate clearance.

Over the first 24 h of ICU, 2100 ml of sodium bicarbonate (8.4%) was administered to normalize plasma pH; activated charcoal and gastric lavage were initially performed in order to eliminate a further possible gastric source of metformin.

CVVHD was continued for 48 h consecutively with complete normalization of lactate levels and improvement of plasma urea and creatinine (Table 1). Hemodialysis was then stopped, as spontaneous urine output was present. At the end of renal replacement therapy, plasma metformin levels reached 4.5 μ/ml, compatible with a normal therapeutic range.

Benzodiazepine sedation was discontinued and ventilatory support was reduced, on the third day of ICU, the patient was weaned from mechanical ventilation, orotracheal tube was removed and spontaneous breathing started 106 h after admission.

With a fully restored ability to communicate, the patient underwent psychiatric evaluation to rule out voluntary intoxication as a suicide attempt. The psychiatrist’s assessment confirmed the absence of dangerous disorders. In fact, from previous medical documents emerged a picture of worsening RF (creatinine 0.16 mmol/l–1.8 mg/dl—Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) glomerular filtration rate 43 ml/min/1.73m²—2 years before intoxication) undervalued by the patient who continued, without referring to the general practitioner (GP) that followed his case of diabetes, with the usual metformin dose regimen that lead to a toxic plasma level over a period of ~1 year: the crisis was triggered by a week of diarrhea and vomiting—diarrhea and vomiting—in an adult diabetic, whose previous status was fit enough to perform moderate intensity activities in his daily life.

Severe lactic acidosis is a life-threatening condition especially when associated to impaired renal function that cripples one of the main pathways of proton elimination.

This patient not only suffered from metformin intoxication, but also from ARF¹⁰ that was present on a background of Stage 3 chronic kidney disease¹¹ which was not previously diagnosed due to patient reluctance in alerting the GP who followed his case. The triggering condition, however, was dehydration caused by diarrhea and vomiting¹² that precipitated a chronic intoxication into a real metabolic crisis.

Correction of metabolic acidosis is central to treatment: sodium bicarbonate seems the most immediate solution, but it failed to produce a sustained increase in blood pH probably due to rapid tissue lactate production in conditions of shock and metformin intoxication. Moreover, it acts only on the extracellular fluid and only indirectly on the intracellular fluid. However, it was the only rapidly available, immediately effective maneuver to revert an otherwise no-return process—cardiac function was, in fact, already so compromised that acidosis lead to cardiac arrest.

Hemodialysis not only corrects acidosis but also removes metformin from plasma reducing lactate production rate. Since the patient was too hemodynamically unstable (norepinephrine continuous infusion was necessary to maintain an acceptable blood pressure level), a CVVHD technique was preferred. The main difference between CVVH and CVVHD¹³ is that the former employs convection as the force which drives solvent and consequently also solutes across a semi-permeable membrane, while the latter exploits diffusion down an electrochemical gradient through a semi-permeable membrane in response to an electrolyte solution running counter current to the blood flow through the filter; diffusive movement occurs via Brownian motion of the solute—smaller molecules (i.e. urea) have greater kinetic energy and are preferentially removed based on the size of the concentration gradient. Solute removal is directly proportional to dialysate flow rate.

**Follow-up**

The patient was discharged from the Department of Nephrology 2 weeks later, with insulin therapy for the underlying diabetes and levels of plasma creatinine at 0.44 mmol/l (5 mg/dl). During the following 2 months, renal function improved up to a creatinine level of 0.31 mmol/l (3.5 mg/dl).

**Discussion**

The peculiar feature of this case lies in its extreme clinical severity and apparently mild manifestations that preceded hospital admission—diarrhea and vomiting—in an adult diabetic, whose previous status was fit enough to perform moderate intensity activities in his daily life.

Two days later, with no sign of residual lactic acidosis, as mild RF persisted (urea 16.33 mmol/l–98 mg/dl and creatinine 0.66 mmol/l–7.53 mg/dl) and the risk of suicide attempt ruled out, the patient was transferred to Department of Nephrology to continue treatment of underlying renal disease.
Currently, none of the data prove that a superior outcome can be achieved with either technique. However, it is rational thinking that as molecular weight (MW) increases diffusive drug clearance declines more than convective clearance. Metformin hydrochloride has a MW of 165.63 Da (similar to urea) that makes it an ideal candidate for hemodialysis instead of hemofiltration, as on a small MW basis, the advantages of diffusion on molecule clearance are more significant.

Spiller et al.14 indicates that shock and extreme acidosis following metformin intoxication are a lethal association in most of the cases. The key to therapeutic success in this case, which shared both these nefarious characteristics, was aggressive medical pH correction15 and early renal replacement therapy to normalize hydrogen ions, electrolytes and counter lactate production by eliminating one of its determining factors: metformin16.

Conclusions
The determining factors that positively affected patient’s survival were a rapid activation and referral to ICU for drastic alkalinizing and renal replacement therapy and a prompt physical response by the patient, whose status was fit enough to tolerate extreme acidosis, shock and the aggressiveness of the necessary therapeutic measures.

The key message of this case is alertness—metformin is a widely used, generally safe anti-diabetic agent, but it keeps a potential risk of severe side effects that can originate from apparently common clinical manifestations that a GP can recognize and promptly treat by adapting anti-diabetic therapy. Consequently, patient education is an important tool in preventing side effects especially in long-term medications, such as metformin.

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Mario Grosoli, MD and Salvatore Perrone, MD offered precious nephrologic consultancy in setting-up and monitoring dialytic treatment and contributed to better understanding of the underlying renal pathology. San Matteo Hospital’s (Pavia, Italy) Poison Control Center provided valuable collaboration in dosing plasma metformin levels and choosing the best therapeutic strategy.

Conflict of interest: None declared.

References