CRITICAL CARE

COMMENTARY

Metformin-induced lactic acidosis: no one left behind

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See related research by Friesecke *et al.*, http://ccforum.com/content/14/6/R226

Abstract

Metformin is a safe drug when correctly used in properly selected patients. In real life, however, associated lactic acidosis has been repeatedly, although rarely, reported. The term metformin-induced lactic acidosis refers to cases that cannot be explained by any major risk factor other than drug accumulation, usually due to renal failure. Treatment consists of vital function support and drug removal, mainly achieved by renal replacement therapy. Despite dramatic clinical presentation, the prognosis of metformin-induced lactic acidosis is usually surprisingly good.

In the previous issue of *Critical Care*, Friesecke and colleagues demonstrate that the survival rate of patients with severe lactic acidosis due to metformin accumulation can be strikingly higher than expected based on the initial clinical evaluation [1].

Metformin is nowadays the first-line drug of choice for the treatment of adults with type 2 diabetes [2]. This drug is the sixth most frequently prescribed in the USA (>50 million prescriptions in 2009) and is taken by almost 1.5% of the Italian population [3,4].

Metformin is a safe drug when correctly used in properly selected patients. In particular, no cases of lactic acidosis (a relatively common side effect of other biguanide compounds) were reported in 347 trials with 70,490 patient-years of metformin use [5]. Real life can differ from research settings, however, and lactic acidosis has been repeatedly, although rarely, observed in patients treated with metformin. The number of inquiries to the Swedish Poison Information Centre for metformin intoxication has increased 10 times during the past decade, with 25 cases of severe lactic acidosis reported in 2007 and 2008 [6]. According to the American Association of Poison Control Centers, metformin may have contributed to 21 fatalities in the USA in 2008 [7]. Forty-nine cases of lactic acidosis and accidental metformin accumulation were reported to the Poison Control Centre of Pavia (Italy) from January 2005 to August 2010, resulting in 11 deaths. Since metformin use is constantly increasing – there has been a 10 to 15% rise in prescriptions per year in the USA and Italy [3,4] – related cases of lactic acidosis may become less rare.

The term metformin-*associated* lactic acidosis refers to any case of lactic acidosis that develops in a patient treated with metformin, with no further mechanistic insight. In most of the cases, however, lactic acidosis cannot be directly attributed to metformin use but rather depends on concomitant low cardiac output, anemia, hypoxemia or liver failure. The term metformin-*induced* lactic acidosis specifically refers to cases that cannot be explained by any major risk factor other than metformin overdose [8]. The distinction between these two entities is sometimes very subtle and metformin accumulation may coexist with other risk factors, all contributing to the pathogenesis of lactic acidosis.

The present case series includes 10 patients admitted to intensive care with lactic acidosis and metformin accumulation due to renal failure [1]. At admission, arterial pH was 6.75 ± 0.13 and lactatemia was 19 ± 5 mmol/l. The Simplified Acute Physiology Score II was 88 ± 23 and the predicted mortality was 96%. Eight (80%) patients had a cardiac arrest during their stay in intensive care. Treatment consisted of vital function support and renal replacement therapy. Despite the dramatic severity of clinical presentation, hospital survival was 50%. Conversely, there were no survivors out of 31 patients with similarly severe lactic acidosis from other causes (mainly cardiogenic, septic or hemorrhagic shock) who were admitted to the same institution during the same period of time.

This finding is in line with previous observations. In 49 patients treated with metformin who developed severe lactic acidosis, survival was 17% among those with no

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drug accumulation (that is, lactic acidosis was actually due to another precipitating event) and was 71% in those with metformin accumulation, despite a similar severity of hyperlactatemia [8]. In another series, one out of 10 (10%) patients with lactic acidosis probably due to metformin accumulation actually died despite an initially predicted mortality of around 55% [9]. We have recently reviewed the data for 24 critically ill patients with lactic acidosis and proven or probable metformin intoxication. Despite an expected mortality of 70%, observed mortality was 21%. Even patients with initial arterial pH down to 6.62, lactatemia up to 33 mmol/l or Simplified Acute Physiology Score II as high as 87 managed to survive to hospital discharge [10].

That lactic acidosis carries a poor prognosis has been known for decades [11]. Lactic acid *per se*, however, is unlikely to be the explanation for this association. Lactate production is indeed an adaptive response to impending energy failure. This response provides some energy and a chance for cells to survive, even when oxygen availability or utilization are defective [12]. Cancer cells in a way provide the best evidence for lactate overproduction being an efficient response to hypoxia. By mainly relying on anaerobic metabolism, malignant cells can not only survive but even proliferate in a hypoxic environment, so that tumor growth can exceed angiogenesis [13]. According to the theory of lactate shuttles proposed by Brooks, lactate may act as an oxidative substrate exchanged between cells and tissues [14]. Acidosis itself may arise as an adaptive response to inadequate energy provision and may extend cellular viability [15].

The prognosis of lactic acidosis primarily depends on the underlying mechanism and on its reversibility. When lactic acidosis is due to metformin accumulation, then renal replacement therapy can efficiently remove the toxic substance (that is, metformin and not lactate!) and prognosis can be surprisingly good. The situation can be much more complex and less easily reversible when lactic acidosis is primarily due to severe hypoxia or tissue hypoperfusion.

Based on present and past observations, one may conclude that the decision to treat (or not to treat) a patient with suspected metformin-induced lactic acidosis cannot be based only on the severity of clinical presentation. We personally believe that treatment of the critically ill patient should always include drug removal, as long as metformin accumulation is thought to be responsible for severe lactic acidosis. Since a plasma metformin dosage is rarely available in most centers, intoxication should be considered highly probable whenever lactic acidosis and renal failure are uncommonly severe, other primary explanations are not evident and chronic metformin use is reported.

Competing interests
The authors declare that they have no competing interests.

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