CRITICAL CARE

COMMENTARY

Metformin overdose: time to move on

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See related research by Protti *et al.*, http://ccforum.com/content/16/5/R180

Abstract

Does metformin-associated lactic acidosis really exist? Despite an old controversy, there is no doubt about it. But do we understand what is going on? Laboratory findings raised several hypotheses explaining the pathophysiology of this disease. The main cause could be an inhibition of either gluconeogenesis or mitochondrial respiratory chain complex I. From bench to bedside, one hypothesis is now confirmed in humans. Metformin poisoning involves, at least partially, a mitochondrial dysfunction.

In this issue of *Critical Care*, Protti and colleagues [1] report the effects of metformin on human platelets both *in vitro* and *ex vivo*. *In vitro* experiments were performed on healthy platelets incubated with increasing doses of metformin, whereas *ex vivo* experiments were done on platelets from patients presenting accidental metformin-induced lactic acidosis. In both situations, platelets' lactate production and mitochondrial functions were measured. *In vitro*, a dose-dependent relationship between metformin concentration and lactate production was found. In both conditions, high levels of metformin decreased mitochondrial respiratory chain complex I activity, mitochondria polarization, and oxygen consumption. *Ex vivo* only, mitochondria respiratory chain complex IV activity declined.

Metformin is a biguanide that has been used as a first-line drug for type 2 diabetes treatment since 1957 in Europe and 1995 in the US [2]. Metformin was reputed to induce lactic acidosis, partly because phenformin, another biguanide, was withdrawn from the market because of an unacceptable rate of this complication [3]. However, numerous clinical studies reported a similar incidence of lactic acidosis in diabetic patients with or without metformin, leading some authors to deny the existence of metformin-associated lactic acidosis [4]. However, in usual clinical practice, metformin contraindications are not often respected [5]. Moreover, physicians do not really monitor adequately their prescription. As a result, numerous publications reported the association between metformin and lactic acidosis [6,7]. When a cause of lactic acidosis such as shock state or acute renal failure is present, the responsibility of metformin could be questioned. But when healthy patients without risk factors develop metformin poisoning leading to lactic acidosis, there is no doubt about this link. However, metformin inhibits hepatic gluconeogenesis in different animal species and decreases mitochondrial respiratory chain complex I activity in different organs [8,9]. Both conditions can lead to lactate accumulation. Until recently, the clinical research on metformin-associated lactic acidosis was limited to retrospective studies describing incidence, risk factors, and supportive treatments. A big step forward was made when the Gattinoni group [10] reported a decrease in oxygen consumption after metformin poisoning in humans, strongly suggesting that metformin was able to induce mitochondrial dysfunction in humans. The study by Protti and colleagues elegantly confirms the implication of mitochondria in the pathophysiology of this disease. But it does not rule out the effects of metformin on gluconeogenesis. Further research is needed to assess the respective parts of these mechanisms.

Of course, the importance of platelet mitochondrial dysfunction *per se* has to be put in perspective. Platelets are probably not involved in lactic acidosis build-up during metformin overdose. However, as demonstrated previously in the pig, platelet mitochondrial dysfunction mirrors the mitochondrial dysfunction in other vital organs [11]. Platelets are more easily accessible than vital organs like the liver or kidney. For research purposes in humans, this approach seems to be promising to evaluate the effects of potential therapies. However, a possible limit to their findings lies in their model. It is not clear whether this model represents acute or chronic overdose. This question is important as they are considered different conditions with different prognoses [12]. Acute intentional poisoning clearly has a better outcome than accidental accumulation.

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Now that serious research on this rare disease has started, we can also imagine improving its care. Currently, the treatment is only supportive: increasing blood pressure with fluid infusion and catecholamines and promoting metformin elimination by renal replacement therapy. Restoring ATP production during energy failure due to mitochondria dysfunction is still challenging. New ideas could come from metabolic manipulations. In severe sepsis, another condition associated with mitochondrial dysfunction, succinate can bypass respiratory chain complex I inhibition and restore oxygen consumption [13]. In isolated cells, succinate is reputed not to cross the plasma membrane, but methyl succinate (a cell-permeant succinate) has been used to bypass metformin blockade of respiratory chain complex I [14]. This intervention led to a reduction of metformin toxicity. This strategy might be a therapeutic modality for metformin overdose in the future.

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

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Published: 25 October 2012

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doi:10.1186/cc11664
Cite this article as: Orban J-C, *et al*.: Metformin overdose: time to move on. *Critical Care* 2012, **16:**164.