CRITICAL CARE

LETTER

Metformin improves survival in intensive care unit patients, but why?

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See related research by Christiansen et al., http://ccforum.com/content/17/5/R192

We read with interest the study by Christiansen and colleagues [1] in the previous issue of *Critical Care*. In a large cohort study, the authors report that among diabetic patients who are admitted to the ICU, the preadmission use of metformin is associated with a lower mortality rate.

Here, we highlight that metformin limits ischemia-reperfusion injury (IRI) and modulates inflammation by increased adenosine receptor stimulation and propose that these mechanisms contribute to the reported survival benefit.

In prospective studies in patients with diabetes, metformin use is associated with lower cardiovascular mortality compared with alternative glucose-lowering agents, suggesting a direct cardioprotective effect of metformin [2]. In animal studies, metformin potently limits myocardial infarct size [2]. This is caused, at least in part, by increased formation of the endogenous nucleoside adenosine [3]. Adenosine receptor stimulation increases tolerance of various organs against IRI and potently modulates inflammation [4]. Indeed, pharmacological elevation of endogenous adenosine modulates the inflammatory response during experimental human endotoxemia [5].

In the study by Christiansen and colleagues, many patients were admitted to the ICU because of cardiovascular diseases or (non-)cardiac surgery. It is likely that in these patients IRI contributes to organ dysfunction. Therefore, we propose that the survival benefit of metformin is caused by limitation of IRI and inflammation due to increased adenosine receptor signaling. Based on this hypothesis, several randomized controlled trials are currently being performed to investigate whether metformin reduces myocardial injury in patients with a myocardial infarction and patients undergoing cardiac surgery (NCT01438723 and NCT01217307). We await with interest the results of these trials.

Author's response

Christian F Christiansen

Metformin and prognosis of critical illness: a question of timing?

I would like to thank Riksen and colleagues for their response to our article and for emphasizing that prevention of IRI could contribute to our finding of a decreased mortality among diabetic ICU patients with preadmission metformin use [1]. The association we found was present in, but not restricted to, the subgroup of patients admitted after elective cardiothoracic surgery, whereas there were no decreased mortality in patients admitted after acute cardiothoracic surgery. Despite statistically imprecise estimates in the subgroups, it raises a question about timing of metformin along the clinical course of critical illness.

In sepsis, there is a proposed bi-phasic inflammatory response, and any effect of potential anti-inflammatory drugs, such as metformin, may be present only if administered before or during the early hyper-inflammatory phase of infection whereas administration during the later hypo-inflammatory phase may be detrimental [6,7]. Similarly, timing along the course of ischemia-reperfusion may be crucial [3]. Studies of drug use in patients at high risk of critical illness (for example, patients undergoing elective major surgery) are therefore important for our understanding of potential beneficial effects,

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as this exposure occurs before the inflammatory response and the ischemia-reperfusion.

Therefore, I find it highly interesting that Riksen and colleagues are conducting trials with metformin administered before coronary artery bypass grafting and after myocardial infarction (NCT01438723 and NCT01217307). Although the magnitude of the inflammatory response is different, the studies will probably provide knowledge about the influence of timing of metformin administration in relation to myocardial injury.

Abbreviations

IRI: Ischemia-reperfusion injury.

Competing interests

The authors declare that they have no competing interests.

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