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Prognosis of extremely severe lactic acidosis in metformin-treated patients with septic shock: continuous (?) renal replacement therapy in the spotlight!

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See related research by Doenyas-Barak et al., http://www.ccforum.com/content/20/1/10

We read with interest the recent paper by Doenyas-Barak et al. [1] comparing the prognosis of extremely elevated plasma lactate levels between metformin (MET)-treated and MET-naive patients with septic shock. The most remarkable finding was a highly significant lower in-hospital mortality (56.8 vs. 88.1 %, $p < 0.0001$) in MET users despite a more explicit risk profile (diabetes, older age) and greater baseline disease severity (higher incidences of cardiovascular disease, acute kidney injury, and underlying malignancy) [1]. The authors briefly elaborate on this unexpected survival benefit by pointing out some potential protective MET-related anti-inflammatory, anti-thrombotic, and cellular effects. However, we believe that the observed difference in mortality rate is most likely due to the more frequent use of renal replacement therapy (RRT) in the MET-treated population (38.6 vs. 21.2 %, $p = 0.13$).

Whereas initiation of RRT is generally stigmatized as a bad prognostic sign in the critically ill, it might be life-saving in MET users presenting with septic shock and severe lactic acidosis. A protective effect of RRT has already been suggested by Peters et al. [2] who found that, despite higher illness severity, the mortality rate in patients with MET-associated lactic acidosis treated with intermittent hemodialysis (IHD) was no different to that of non-dialyzed subjects. Experts recommend RRT at lactate concentrations >20 mmol/L or pH ≤7.0, in case of shock or decreased level of consciousness, and when standard supportive measures fail [3]. Early IHD is the preferred mode of treatment. For several reasons, however, continuous RRT (CRRT) is thought to be physiologically more appropriate than IHD. First, because of its low molecular weight and minimal protein binding, MET is equally (highly) eliminated by ultrafiltration (convection) as compared to dialysis (diffusion). Second, and more importantly, its large volume of distribution within a two-compartment pharmacokinetic model implies that MET may be more effectively cleared by prolonged RRT. This was corroborated by Keller et al. [4] who recently showed a dramatic reduction of metabolic acidosis and decrease of MET plasma concentrations within the first 24 h after initiating CRRT in patients with MET-induced lactic acidosis, followed by normalization on the second day in all subjects. Finally, consensus exists that CRRT is better tolerated in hemodynamically unstable patients, and is also associated with a higher rate of renal recovery compared with IHD [5]. This will certainly benefit septic MET-imbedded patients who often present with catecholamine-dependent septic shock and faltering or lost kidney function.

Authors' response

K. Doenyas-Barak, I. Beberashvili and S. Efrati

The role of RRT in the treatment of lactic acidosis in general, and in metformin-associated lactic acidosis (MALA) in particular, has been the subject of several trials. Due to the low molecular weight of lactate (90 Da, which is very similar to urea), and its easy removal by RRT, patients with severe lactic acidosis are good candidates for RRT [6]. However, lactate itself is not toxic, and data regarding

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the yield of RRT in patients with severe lactic acidosis are scarce. In MALA, RRT may contribute to both lactate and metformin removal. Unfortunately, data regarding the effect of RRT in the setting of MALA are also limited, being based mostly on observational studies or very small trials. In one of them, although improved prognosis of patients requiring RRT was not actually demonstrated, the authors believed that the prognosis might have been worse [2]. However, even though reliable data comparing RRT given "prophylactically" at an early stage vs. RRT given according to classical clinical indications (as determined by the treating nephrologist) do not exist, some experts still strongly recommend the earliest possible initiation of RRT [3].

Following the letter of Drs. Honore and Spapen, we performed further statistical analysis of our study cohort to evaluate whether more frequent RRT in the metformin-treated group may explain the survival benefit. Multivariate Cox regression analyses were redone for the evaluation of adjusted hazard ratios (HRs) of metformin treatment, with RRT added to the confounders (in addition to age, gender, diabetes, hypertension, ischemic heart disease, cerebrovascular attack, malignancy, creatinine, and Acute Physiology and Chronic Health Evaluation (APACHE) II score). The effect of the hazard related to metformin treatment remained statistically significant (HR = 0.18; 95 % confidence interval 0.03–0.92; $p = 0.04$). Thus, the use of RRT does not appear to explain the protective effect of metformin in the current cohort of patients [1].

Another unresolved issue relates to the preferred RRT modality, and to whether CRRT may be physiologically more appropriate than IHD for MALA patients. CRRT is the preferred modality in patients who are hemodynamically unstable and cannot tolerate IHD due to blood pressure fluctuations. However, for other MALA patients, hemodialysis may be the preferred approach since metformin clearance is less effective under the convective treatment used in CRRT [7]. Unfortunately, the size of our study population was not sufficient to address the preferred RRT modality for MALA patients.

Abbreviations

CRRT: continuous renal replacement therapy; HR: hazard ratio; IHD: intermittent hemodialysis; MALA: metformin-associated lactic acidosis; MET: metformin; RRT: renal replacement therapy.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

PMH and HDS designed the paper, participated in drafting the manuscript, and read and approved the final version.

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