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LETTER TO THE EDITOR

Could metformin be used in patients with advanced chronic kidney disease?

To the Editor:

We read with great interest the review article by Chowdhury et al.[1] Over the last 5 years there has been great interest in relaxing the contraindication of renal impairment for prescribing metformin.[2,3] We have examined the use of metformin in patients with advanced chronic kidney disease (CKD).[4,5] Chowdhury et al.[1] referenced our publication of a population pharmacokinetic model, which we used to simulate possible dosing regimens for patients with all grades of renal function (down to creatinine clearances of 15 mL/min).[5] The goal of this analysis was to ensure that the 95th percentile peak plasma concentrations of metformin did not exceed 5 mg/L. These dosing regimens have been assessed by MedSafe (the New Zealand medicines regulatory agency) and have been incorporated into their metformin product label.[6] We encourage other regulatory bodies to consider making similar changes.

Metformin is largely eliminated unchanged by the kidneys[7] and, consequently, a major concern is that patients with renal impairment will accumulate metformin and this could lead to the development of lactic acidosis, a serious adverse effect of metformin. A putative metformin plasma concentration of 5 mg/L has been suggested as being indicative of significant risk of metformin-associated lactic acidosis (MALA).[8] We and others have suggested that metformin at therapeutic dosages is not a causative agent, even at concentrations >5 mg/L, but rather is an innocent by-stander.[9,10] Many patients on metformin have comorbidities that increase the risk of lactic acidosis. Indeed, a recent retrospective study showed that, while metformin was significantly associated with an increased risk of the need for acute dialysis, this risk was conditional upon concomitant "patient frailty."[11] This implies that secondary characteristics that predispose a patient to enhanced lactate concentrations, such as age, renal function and cardiac failure, work in conjunction with metformin concentrations to induce damage.

Our metformin dosing regimen in acute kidney injury has also been supported by Hung et al.[12] Their study showed the adverse effects of "over-dosing" of metformin in the setting of advanced chronic kidney disease, showing that metformin increased all-cause mortality in a dose-dependent manner in patients with CKD stage 5.[12] The design of novel formulations of metformin that reduce systemic exposure to metformin, such as a delayed release form absorbed from the distal small intestine,[13] could further increase the safety of metformin in renally compromised patients.

In addition to monitoring metformin plasma concentrations and renal function, a practice we and others encourage,[6] we agree with the authors' guidance on counselling patients with advanced CKD for "sick day rules."[1] One of the common signs patients reference prior to the onset of MALA is severe gastrointestinal symptoms (vomiting, diarrhoea).[9] This should be a red-light warning for patients to cease metformin use and seek medical attention.

Chowdhury et al.[1] conclude that more studies examining the safety and efficacy of metformin in patients with advanced CKD are required. We have recently completed a small pharmacokinetic study on metformin in patients on chronic haemofiltration over 12 weeks.[15] Furthermore, we propose to study metformin in a larger haemofiltration patient cohort, for a longer duration, our aim being to determine the optimum metformin dosing regimen required in this high-risk patient group (www.anzctr.org.au, ACTRN12616000675426). We, too, believe that the cardiovascular benefits associated with metformin use[14] far outweigh the risks of MALA, particularly if the patients are monitored carefully.

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Conflict of interest

The authors have no conflicts of interest to declare.

Author contributions

S. Kumar drafted the letter; all authors contributed to the letter.

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