Clarifying the relationship between metformin, acute kidney injury and lactic acidosis

Bell, Samira; Soto-Pedre, Enrique; Connelly, Paul; Livingstone, Shona; Pearson, Ewan

Published in:
Nature Reviews Nephrology

DOI:
10.1038/nrneph.2017.172

Publication date:
2017

Document Version
Peer reviewed version

CORRESPONDENCE

Clarifying the relationship between Metformin, Acute Kidney Injury and Lactic Acidosis

Samira Bell[1,2], Enrique Soto-Pedre[3], Paul Connelly[3], Shona Livingstone[4] & Ewan Pearson[3]

We read, with interest, the News and Views article by C. Rhee and K. Kalanter-Zadeh (Diabetes mellitus: Complex interplay between metformin, AKI and lactic acidosis. *Nat. Rev. Nephrol*. **13**, 521–522; 2017)[1], which discusses our recent work looking at the relationship between metformin, acute kidney injury (AKI), and lactic acidosis[2,3]. In response to this discussion of some of our findings we would like to highlight several points

First, Connelly *et al*. demonstrated that 80% of lactic acidosis within the study cohort occurred in the presence of AKI[3]. In view of the effectiveness of treatment and increasing evidence of the beneficial cardiovascular effects of metformin, we feel that metformin should be only temporarily discontinued in patients with a condition that predisposes them to acute AKI; this advice is similar to the advice given for ACE inhibitors and angiotensin receptor blockers.

Second, although we acknowledge the difficulties of accurately identifying metformin-associated lactic acidosis (MALA) cases in observational studies, we do not agree that the crude incidence rate of lactic acidosis observed in the study by Connelly *et al*. is biased because it differs from rates reported by others. Instead, we would like to emphasize that crude incidence rates disregard the structure of the population. Thus, comparing crude incidence rates alone can be misleading before standardization is carried out to remove the effect of differential structures in populations under comparison.

Third, it was also suggested that the absence of a 'new-user' design in the study by Bell et *al*.[2] may not have accounted for patients who stopped using metformin or died due to its adverse effects

before study entry, biasing results towards a protective effect. Our study population comprised of 63% incident users over a long period, making survivor bias a less likely explanation for our findings.

Fourth, the elevated risk of developing AKI that is associated with 'ever' having been on or currently being on metformin is due to within and between person allocation bias, where being prescribed metformin is a marker for other co-morbidities making the patient more vulnerable to AKI**.** The fact that AKI incidence is not elevated in patients during periods on the drug compared with periods off the drug, suggests that the drug itself is not increasing the risk of AKI.

Finally, we do not agree with the recommendation made by C. Rhee and K. Kalanter-Zadeh that the use of metformin should be restricted in patients with chronic kidney disease (CKD), particularly in view of the increasing evidence base that supports metformin safety in CKD[4,5]. We eagerly await further pharmacokinetic studies on the safety and efficacy of metformin in these patients.

Affiliations

[1]Renal Unit, Ninewells Hospital, Dundee, DD1 9SY

[2]Population Health Sciences , School of Medicine, The Mackenzie Building, Kirsty Semple Way, Dundee, DD2 4BF

[3]Division of Molecular & Clinical Medicine, Level 5, Mailbox 12, Ninewells Hospital and Medical School, Dundee, DD1 9SY

Correspondence to: SB samira.bell@nhs.net

1. Rhee CM, Kalantar-Zadeh K. Diabetes mellitus: Complex interplay between metformin, AKI and lactic acidosis. Nature reviews Nephrology. 2017 Sep;13(9):521-2. PubMed PMID: 28736433.

2. Bell S, Farran B, McGurnaghan S, McCrimmon RJ, Leese GP, Petrie JR, et al. Risk of acute kidney injury and survival in patients treated with Metformin: an observational cohort study. BMC nephrology. 2017 May 19;18(1):163. PubMed PMID: 28526011. Pubmed Central PMCID: 5437411.

3. Connelly PJ, Lonergan M, Soto-Pedre E, Donnelly L, Zhou K, Pearson ER. Acute kidney injury, plasma lactate concentrations and lactic acidosis in metformin users: A GoDarts study. Diabetes, obesity & metabolism. 2017 Apr 21. PubMed PMID: 28432751.

4. Ekstrom N, Schioler L, Svensson AM, Eeg-Olofsson K, Miao Jonasson J, Zethelius B, et al. Effectiveness and safety of metformin in 51 675 patients with type 2 diabetes and different levels of renal function: a cohort study from the Swedish National Diabetes Register. BMJ open. 2012;2(4). PubMed PMID: 22798258. Pubmed Central PMCID: 3400073.
5. Roumie CL, Hung AM, Greevy RA, Grijalva CG, Liu X, Murff HJ, et al. Comparative effectiveness of sulfonylurea and metformin monotherapy on cardiovascular events in type 2 diabetes mellitus: a cohort study. Annals of internal medicine. 2012 Nov 6;157(9):601-10. PubMed PMID: 23128859. Pubmed Central PMCID: 4667563.

Competing interests statment

The authors declare no competing interests.