International Urology and Nephrology (2019) 51:1229–1230
https://doi.org/10.1007/s11255-019-02136-y

NEPHROLOGY - ORIGINAL PAPER

Lactic acidosis due to metformin in type 2 diabetes mellitus and chronic kidney disease stage 3–5: is it significant?

Ravindra Attur Prabhu[1] · Aswani Srinivas Mareddy[1] · Shankar Prasad Nagaraju[1] · Dharshan Rangaswamy[1] · Vasudeva Guddattu[2]

Received: 4 March 2019 / Accepted: 26 March 2019 / Published online: 8 April 2019

Abstract

Purpose To study the incidence of lactic acidosis due to metformin in patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) stage 3–5.

Methods We estimated plasma lactate in patients of CKD stage 3 and worse who were continuing metformin on their own prior to stopping the drug.

Result Of 40 patients included, median duration of T2DM was 60 months (interquartile range IQR 24–120). The mean serum creatinine was 309.4 ± 159.1 µmol/L and mean eGFR was 27.82 ± 12.93 mL/min/1.73 m^2 with 3 (7.5%), 16 (40%), 11 (27.5%) and 10 (25%) in CKD stages 3a, 3b, 4 and 5, respectively. They were receiving metformin for a median duration of 24 months (IQR 12.5–60), an average dose of 896 ± 350 mg per day. The median of plasma lactate was 1.36 mmol/L (IQR 1.11–1.75 mmol/L) with three (7.5%) having levels above normal, two (20%) in CKD stage 5 and one (9.1%) in stage 4.

Conclusion Metformin can be safely used in CKD stage 3 and with regular measurement of plasma lactate in later stages.

Keywords Chronic kidney disease · Lactic acidosis · Metformin · Type 2 diabetes mellitus

Introduction

Metformin is the recommended first-line glucose-lowering therapy for type 2 diabetes mellitus (T2DM), but its accumulation can potentially cause lactic acidosis in later stages of CKD [1]. We studied the presence of lactic acidosis in patients with CKD stage 3–5 who had inadvertently continued metformin on their own.

Materials and methods

After institutional ethics committee clearance and informed consent, consecutive patients of T2DM visiting the outpatient department of a tertiary referral hospital with estimated glomerular filtration rate (eGFR) of < 60 mL/min/1.73 m^2 as measured by serum creatinine-based standard CKD-EPI formula and who were inadvertently continuing metformin on their own were included. Those with sepsis, malignancies, cardiac failure and other medications which could potentially cause lactic acidosis were excluded. After physical rest of 30 min, venous blood was drawn. Plasma lactate was measured by a lactate oxidase enzyme-based colorimetric assay (normal range 0.49–2.2 mmol/L) and metformin stopped. CKD was staged using Kidney Disease Improving Global Outcomes (KDIGO) classification into categories 3a, 3b, 4 and 5 based on eGFR (mL/min/1.73 m^2).

Data were analyzed on SPSS version 15 for descriptive statistics, and Spearman's co-relation was used to compare the relation between eGFR and plasma lactate.

Results

Of the 40 patients included, 7 (17.5%) were females, the mean age was 56 ± 8.24 years and the median duration of T2DM was 60 months (interquartile range IQR 24–120). The mean serum creatinine was 309.4 ± 159.1 µmol/L and mean

✉ Ravindra Attur Prabhu
aravindraprabhu@gmail.com

[1] Department of Nephrology, Kasturba Medical College and Hospital Manipal, Manipal Academy Higher Education, Madhav Nagar, Manipal, Udupi, Karnataka 576104, India

[2] Department of Statistics, Prasanna School of Public Health, MAHE, Udupi, India

eGFR was 27.82 ± 12.93 mL/min/1.73 m^2 with 3 (7.5%), 16 (40%) and 11 (27.5%), 10 (25%) in CKD stages 3a, 3b, 4 and 5, respectively. They were receiving metformin for a median duration of 24 months (IQR 12.5–60), an average dose of 896 ± 350 mg per day. The median of plasma lactate was 1.36 mmol/L (IQR 1.11–1.75 mmol/L) with three (7.5%) asymptomatic patients having levels above normal, two (20%) in CKD stage 5 and one (9.1%) in stage 4. There was no correlation between eGFR and plasma lactate.

Discussion

Metformin, a glucose-lowering drug of biguanide class, works by entry into cells through organic cation transporters, activating adenosine monophosphate (AMP)-dependent protein kinases, reducing hepatic glucose production through antagonism of hepatocyte cyclic AMP generation by glucagon with some increase in peripheral glucose utilization, promoting weight loss and may reduce cardiovascular risk. It is inexpensive and has favorable adverse effect profile [1]. Concern about development of lactic acidosis contraindicates its use in CKD stage 4 and greater and caution is advised in CKD stage 3 [2]. However, stopping this drug causes rise in glycosylated hemoglobin and body mass index [3]. The prevalence of CKD in diabetes mellitus [4] being up to 25% limits the use of metformin in this population. Controlled trials are not feasible and evidence for its effect in CKD is available through large registry data correlating hospitalizations for acidosis with metformin use [5]. A Cochrane systematic review mentions absence of evidence for lactic acidosis with metformin use [6], but direct evidence in further stages is available only through case reports and series wherein 5.4% of patients of lactic acidosis receiving metformin were of end stage renal disease [7]. Metabolic acidosis seen in CKD may also be due to uremia. We found normal plasma lactate levels in CKD stage 3, similar to findings from a community-based cohort [5]. Plasma lactate was normal in 90.9% and 80% of those with CKD 4 and 5, respectively. Overall, we found high plasma lactate in 3/40 (7.5%), less than that seen in previous studies which may have included patients with other risk factors for lactic acidosis [8]. Limitations of this study are small sample size and lack of a control group. Pragmatic observational trials such as this of a larger number of patients will help in further assessing the safety of this useful drug.

We conjecture that metformin can be safely used in CKD stage 3 and with close monitoring of plasma lactate in stages 4 and 5.

Acknowledgements This study was funded through a seed grant from Manipal Academy of Higher Education, India.

Author contribution RAP: study concept and design, ASM: acquisition of data, SPN and DR: preparation of manuscript, VG: statistical analysis. All authors contributed to the preparation of the report and approved the final version. We have included a conflict of interest disclosure statement in the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Statement of ethics All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Powers AC, Niswender KD, Rickels MR. Diabetes Mellitus: Management and Therapies. In: Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J (eds) Harrison's Principles of Internal Medicine, 20e New York, NY: McGraw-Hill. http://accessmedicine.mhmedical.com.kmcezproxy.manipal.edu/content.aspx?Bookid=2129&sectionid=192288412. Accessed 01 Nov 2018
2. Inzucchi SE, Lipska KJ, Mayo H, Bailey CJ, McGuire DK (2014) Metformin in patients with Type 2 diabetes and kidney disease: a systematic review. JAMA 312(24):2668–2675. https://doi.org/10.1001/jama.2014.15298
3. Rachmani R, Slavachevski I, Levi Z, Zadok B, Kedar Y, Ravid M (2002) Metformin in patients with type 2 diabetes mellitus: reconsideration of traditional contraindications. Eur J Int Med 13(7):428. https://doi.org/10.1016/S0953-6205(02)00131-0
4. Centers for Disease Control and Prevention. Chronic kidney disease surveillance system—United States. Website. http://www.cdc.gov/ckd. Accessed 6 Nov 2018
5. Lazarus B, Wu A, Shin J et al (2018) Association of Metformin use with risk of lactic acidosis across the range of kidney function: a community-based cohort study. JAMA Int Med 178(7):903–910. https://doi.org/10.1001/jamainternmed.2018.02925
6. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE (2010) Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev. https://doi.org/10.1002/14651858.cd002967.pub4
7. Yeh HC, Ting IW, Tsai CW, Wu JY, Kuo CC (2017) Serum lactate level and mortality in metformin-associated lactic acidosis requiring renal replacement therapy: a systematic review of case reports and case series. BMC Nephrol 18(1):229
8. van Berlo-van de Laar IR, Vermeij CG, Doorenbos CJ (2011) Metformin associated lactic acidosis: incidence and clinical correlation with metformin serum concentration measurements. Journal of clinical pharmacy and therapeutics 36(3):376–382