Open Access Editorial

Journal of Renal Endocrinology

J Renal Endocrinol 2017;3:e09.

http://www.jrenendo.com

Nickan Research Institute

Metformin-associated lactic acidosis in patients with renal insufficiency

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In the last few decades, metformin has been used to treat diabetes mellitus (type 2) which belongs to the family of biguanide drugs. Metformin drives from the roots of *Galega officinalis* that used to be utilized in the treatment of diabetes in traditional medicine (1).

In addition, it is easily absorbed in the small intestine and has a peak plasma level within two hours of administration. Renal excretion of metformin consists of both filtration from the glomeruli and secretion from the renal proximal tubules without being metabolized or bound to a protein (1,2). Metformin is also the end-metabolite of some amino acids such as arginine that can be detected in the urine (3).

Although metformin is widely used as the first-line drug option to reduce glucose levels in individuals with diabetes mellitus (type 2), it is contraindicated in patients with renal dysfunction due to the possibility of developing lactic acidosis (LA) (3). Individuals with eGFRs (estimated glomerular filtration rates) of 30–60 mL/min/1.73 m^2, stage three of chronic kidney disease (CKD), may experience a 75% reduction in the filtration (2,3). It has been shown that the therapeutic level for this drug is 0.7 (0.3–1.0) mg/L while the upper therapeutic limit level is 5 mg/L (4).

For decades, there has been a concern about developing LA with metformin intake. LA is detected by a serum metformin level of more than 5 μg/mL (2). LA has two types. The first type is anaerobic LA which is caused by lactate overproduction during the production of adenosine triphosphate (ATP) in situations where there is a lack of oxygen and is also frequently observed in cardiovascular collapse. Additionally, this condition may be detected in other conditions such as sepsis, cardiac failure, hypotension, and shock. On the other hand, the second type of LA is the aerobic type which is caused by decreased usage of lactate due to impaired elimination by oxidation or gluconeogenesis. This type is frequently observed in conditions such as alcohol consumption, metformin intoxication, malignancies, hepatic disease, and diabetes. Accumulation of lactate results in severe metabolic acidosis and is associated with poor outcomes and increased mortality in individuals with renal dysfunction (2-6).

Implication for health policy/practice/research/ medical education

Metformin, a diabetes mellitus (type 2) drug, is contraindicated in patients who have renal dysfunction due to the possibility of developing lactic acidosis (LA). Metformin-associated LA is caused by hepatic and mitochondrial dysfunction, which leads to the production of lactate acid. Hemodialysis is the treatment of choice in metformin-associated LA.

The mechanism of LA that is caused by metformin is conducted by hepatic blockage of peripheral oxidative-phosphorylation and mitochondrial dysfunction which leads to the blockage of oxygen usage and impaired gluconeogenesis and glycogenolysis and, in turn, the production and accumulation of lactate acid (3, 6).

The treatment of metformin-associated-LA and toxicity is renal dialysis. Although hemodialysis is incapable of removing a substantial amount of lactate in patients with severe metformin-associated-LA, it improves the acid-base balance and outcomes in these patients (2, 6).

Authors' contribution

Primary draft by HN. Scientific edit by SH. All authors read and signed and approved the final paper.

Conflicts of interests

The authors declare that they have no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

None.

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Received: 17 August 2017, Accepted: 14 November 2017, ePublished: 28 November 2017

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Citation: Hassanzadeh S, Nasri N. Metformin-associated lactic acidosis in patients with renal insufficiency. J Renal Endocrinol. 2017;3:e09.