Journal of Nephrology & Therapeutics

Inadvertent Use of Metformin in a Peritoneal Dialysis Patient: Case Report and Literature Review

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Abstract

Background: Metformin has been a main stay medication in the treatment of type 2 diabetes mellitus. However, its use has been limited by its potential risk of metabolic acidosis in chronic kidney disease. Although this been anecdotally proposed, there have been no studies suggesting the effects of metformin in end stage renal failure, especially in the setting of peritoneal dialysis. We submit a case of metformin inadvertently used in end stage renal failure, without evidence of metabolic acidosis.

Case presentation: A 54 year old man with known type 2 diabetes mellitus presented late to our service with end stage renal failure. He had been on metformin at time of diagnosis of end stage renal failure. Although initially ceased on admission, metformin was inadvertently restarted on discharge from another hospital where he had been transferred for a tenchkoff catheter insertion. This issue was only realised 10 days later following an incidental medication review. He had already commenced peritoneal dialysis at this stage. He was asymptomatic and there was no evidence of metabolic acidosis. We hypothesise that Metformin use in end stage renal failure with dialysis may not be as harmful. To our knowledge, this is the first case report suggesting the use of metformin in such a setting.

Conclusion: Metformin has long been associated with the potential adverse effect of metabolic acidosis. However, our case report suggests further investigation into the potential use of metformin in end stage renal failure requiring dialysis, particularly those requiring peritoneal dialysis. In light of its overwhelming beneficial mortality effects, further studies would need to confirm the safety of such measures, including the need for a creation of an international registry.

Keywords: Dialysis; Metformin; Lactic acidosis; Chronic kidney disease

Background

Cardiovascular disease remains the most common cause of death in patients with type 2 diabetes mellitus, accounting for 52% deaths [1]. Patients with chronic kidney disease have evidence of dyslipidaemia, accelerated atherosclerosis and increased cardiovascular risk [2].

Case Report

In September, 2014, a 54 year old male with a long-standing 20 year history of type 2 Diabetes Mellitus, presented to emergency department with fluid overload. Serum creatinine was 1370 μmol/l (eGFR 3 ml/min/1.73 m²) and urea 45 mmol/L. No priori blood tests were available and as renal tract ultrasound showed small kidneys, unsuitable for biopsy and urine protein creatinine ratio suggested nephritic range proteinuria (>300 g protein/mmol Creatinine), he was presumed to have diabetic nephropathy. At the time of presentation, is medications were Metformin XR 1 g BD, Valsartan 320 mg OD & Frusemide 40 mg OD. He had apparently commenced on metformin 15 years ago, and the dose remained unchanged since it was started, although the preparation had been changed from immediate release to extended release.

His lactate on admission was within normal range (1.1 mmol/L). On admission, metformin was ceased and as his blood sugar levels remained consistently <10 mmol/L, he remained off anti-diabetic medication. The plan was to commenced acute peritoneal dialysis and he was transferred to our local tertiary hospital for tenchkoff catheter insertion. However, he was inadvertently discharged home on his prior dose of metformin XR 1 g BD in a dosage administration pack. This error was noted 10 days later on an incidental medication review. He had remained well throughout and bloods tests revealed no evidence of metabolic acidosis. We had subsequently ceased Metformin at this stage.

Discussion

Metformin hydrochloride is recommended by the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) as first line therapy for type 2 diabetes mellitus. It improves glucose tolerance, lowering both basal and postprandial plasma glucose. It decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilisation. It is noted to have additional modest improvement in lipid profiles. Unlike other oral hypoglycaemic agents, metformin does not usually cause hypoglycaemia (unlike the sulfonylureas or glinides) or weight gain (unlike the thiazolidinediones, sulfonylureas, and glinides). Furthermore, it has a dramatic 42% risk reduction in diabetes related mortality [3]. It is the only oral hypoglycaemic agent to significantly reduce the risk of mortality and myocardial infarction [4]. The additional benefit of combinations of metformin and insulin secretagogue is a reduction of HbA1c between 1.5% to 2.2% in patients sub-optimally controlled by diet and exercise [5].

Metformin is freely water soluble molecule which is excreted unchanged in the urine and does not undergo hepatic metabolism

(no metabolites have been identified in humans) or biliary excretion. Its renal clearance is approximately 3.5 times greater than creatinine clearance, indicating that tubular secretion is the major route of elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In patients with impaired renal function, the blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

Contra-indications for the use of metformin include renal impairment, cardiac or respiratory insufficiency (likely contributing towards tissue hypoxia), history of lactic acidosis, severe infection, liver disease, alcohol abuse and use of intravenous radiographic contrast agents.

The most common adverse reactions following metformin administration include gastrointestinal side effects, i.e. diarrhoea, nausea and vomiting, (affecting 1-30% of patients) are usually transient when metformin is started. Unfortunately, diarrhoea remains the most common cause for discontinuation of metformin [6]. The risk of hypoglycaemia is low. However, this has been reported in 10% of cases of metformin poisonings involving intake >50 g. No causal association has been proved.

Lactic acidosis is rare but the most dangerous claimed effect. It is defined as elevated serum lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. Even without metformin, Type 2 Diabetes has been noted to predispose hyperlactinaemia, with patients having double the lactate levels compared to healthy individuals [6].

The suspected incidence of acidosis is 0-0.084 cases/1000 patient years [7]. However, there were no reports of lactic acidosis in 347 trials with 70,490 patient-years of metformin use [8]. When occurs, it is reported to be fatal in approximately 50% cases. However, great controversy exists regarding whether the use of metformin is a cause or coincidence of lactic acidosis in diabetic patients. Case reports of acidosis have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and hypo-perfusion states, confounded in the setting of multiple medical problems and medications. Interestingly, Brown et al. demonstrated a similar lactic acidosis event rate of 9.7 per 100,000, in patients prior to the introduction of metformin [9].

The proposed mechanism for metformin induced lactic acidosis (MILA) is via conversion of glucose to lactate in the splanchnic bed of the small intestine, through shifts in intracellular reduction and oxidation reactions from aerobic, to anaerobic metabolism. Furthermore, metformin reduces activity of pyruvate carboxylase inhibiting conversion of lactate, pyruvate and alanine leading to additional lactate substrates [10]. The therapeutic trough level for metformin is presumed to be 0.7 mg/L, with an accepted upper limit <5 mg/L [11]. When metformin is implicated as the cause of lactic acidosis, levels greater than 5 mg/L are generally found. However, there is no association between toxicity level and mortality. It has been suggested that the main determinant of levels of hyper-lactatemia is the degree of underlying haemodynamic compromise rather than the metformin concentration per se [12,13].

At present, management of suspected metformin induced lactic acidosis is largely supportive. If acute poisoning is suspected, gastrointestinal decontamination can be performed using activated charcoal. Metformin is readily removed by haemodialysis (clearance up to 170 ml/min), which also corrects acidosis. It is unclear if metformin is as readily removed by peritoneal dialysis.

Curiously, Heath describes a similar situation with concerns of MILA however in the setting of heart failure [14]. With meta-analysis review, this situation was overturned following results of reduced mortality and hospital admission with no evidence of lactic acidosis [15]. With potential further review, this may also be the possibility with end stage renal failure with those requiring dialysis.

Conclusion

Our patient had end stage renal failure and was taking a reasonably high dose of metformin, yet did not develop obvious lactic acidosis. Given the precautions associated with metformin and chronic kidney disease, this would have been the expected course of events. We reviewed the literature surrounding metformin and lactic acidosis, and found that this effect to have multifactorial causes when present. We are not aware of any other similar case reports but given the clearance of metformin on dialysis, feel that the time is now ripe to formally examine the safety of metformin use in dialysis patients, particularly peritoneal dialysis, and potentially haemodialysis. We further suggest the creation of an international registry for patients with chronic kidney disease stage IV and V for patients who have been known to have been on metformin. This would allow investigation for potential safety and usage in other stages of renal failure.

Informed consent was obtained from the patient. The authors can provide this on further request. We the authors declare no conflict of interest.

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