CLINICAL VIGNETTE

METFORMIN USE IN CHRONIC KIDNEY DISEASE: A Dilemma

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Case Report

A 60-year-old man was well until he developed severe flu-like symptoms along with polyuria and polydipsia. Eventually the URI resolved but the polyuria and polydipsia persisted. He was seen by a primary care physician who diagnosed new onset diabetes mellitus and started him on metformin 500 mg per day. The next day, his blood sugar returned at 834 mg/dL and he was referred to the emergency room. In the emergency room, his labs included glucose of 689 mg/dL, BUN 43 mg/dl, and creatinine of 3.36 mg/dL. He was hydrated and started on insulin. Subsequently he was found to have an obstructive uropathy from BPH which was treated with an alpha-blocker and his creatinine fell to 1.62 mg/dL. Over the 3 months following his initial diagnosis of diabetes mellitus, he began exercising regularly, changed his diet, and lost approximately 30 pounds. His A1C fell from 12.9 to 5.9%. The option of discontinuing insulin and switching to oral agents was presented to the patient at which time he informed his endocrinologist, that he had never stopped taking the metformin which had been initially prescribed.

Discussion

This patient's care presents an opportunity to review the issue of the use of metformin in chronic kidney disease. Traditionally, recommendations have been that metformin should not be used, and if in use, discontinued in men with a creatinine of 1.5 or above and in women with a creatinine of 1.4 or above[1]. But where do these recommendations come from and what are they based on? What would an evidence-based recommendation suggest based on available studies? This topic has been addressed in a variety of recent reviews and studies, the ideas of which are discussed below.

Metformin is a medicine in the class of drugs known as biguanides used for the treatment of type 2 diabetes. The initial medicine available in this class was phenformin, which was well known to cause lactic acidosis, a condition with a mortality rate of approximately 50%. Phenformin was eventually withdrawn from the market in the U.S. as well as in most countries because of this life-threatening problem. When metformin was introduced in 1995, it was assumed that it would have the same side effect and that because it is renally eliminated, the level of renal function would be important. Therefore the US Food and Drug administration labeling established creatinine limits for its use. The creatinine levels deemed safe for use of metformin were based on a calculation of the ability to remove 3 grams of metformin at steady state levels within 24-48 hours. Even at this dose of metformin which is higher than doses commonly prescribed, the theoretical safe level of creatinine was 1.8-2.0 mg/dl, not the slightly lower levels cited above[2].

Despite the supposition that metformin like its predecessor, phenformin, would cause lactic acidosis, there was no sound reason to make that assumption. Phenformin inhibits hepatic oxidative phosphorylation, thereby increasing the level of lactate production by anaerobic pathways. Metformin does not alter the intracellular anaerobic lactate production[3-5].

Cases of metformin associated lactic acidosis, although rare, have been reported. Studies have looked at the correlation between metformin associated acidosis and the extent to which the acidosis was actually due to lactic acidosis and whether there were other underlying factors which would explain lactic acidosis when present. A review by Stades et al showed evidence that lactic acidosis could be explained by the underlying diseases (cardiac, pulmonary, hepatic or renal) and that there was no correlation between lactate levels and metformin levels. Metformin levels also did not correspond with mortality. Overwhelmingly, the conclusions were that most cases of metformin associated lactic acidosis were probably not related to metformin[6-10].

In one large case control analysis based on the U.K.-based General Practice Research Database[11] covering approximately 50 million people, 50,048 patients were identified who had received metformin or sulfonylureas and their rates of lactic acidosis were compared. The conclusion was that there were 3.3 episodes of lactic acidosis per 100,000 person-years among metformin users. However, there were 4.8 cases of lactic acidosis per 100,000 person-years among sulfonylurea users so it doesn't appear that the lactic acidosis can be attributed to metformin any more than it can be attributed to sulfonylureas.

In 2010 Salpeter et al[12] performed an electronic database search of prospective trials and observational cohort studies in patients with type 2 diabetes which evaluated metformin compared to placebo or any other glucose lowering therapy. The data included 347 studies. There were no cases of lactic acidosis in either the 70,490 patient-years of metformin users or in 55,491 patient- years of the non-metformin users. There was no difference in lactate levels between the groups. In this analysis, 53% of prospective studies allowed for inclusion of renal insufficiency. This also shows that the incidence of lactic acidosis is extremely rare.

Studies of metformin in patients with chronic kidney disease are limited and more research is needed in this area, but our case demonstrates that metformin is already used in practice in patients with mild to moderate kidney disease. This has been shown by various studies[13, 14].

Given all of the above, what should our approach be to patients who have kidney disease and would benefit from the use of Metformin?

The proposed recommendations from Lipska et al. for metformin use are based on eGFR, which is usually a more reliable measure of kidney function. One set of recommendations is to continue metformin for all patients with eGFR's above 30 mL/min per 1.73 m2.and to stop it if eGFR is below 30^2 the dose of metformin should be reduced (e.g. by 50% or to half maximal dose) if eGFR is between 30- 45 and renal function should be monitored every 3 months. Metformin may be continued or started with eGFR 45 or above, but renal function should be monitored every 3-6 months. Although this approach is somewhat more relaxed than the common current recommendations of discontinuing metformin at 1.5 and 1.4 mg/dL for men and women respectively, based on the absence of evidence for a connection between metformin and lactic acidosis, even these recommendations are probably restrictive. Current proposed recommendations based on eGFR are consistent with the National Institute of Health and Clinical Excellence guidelines in the U.K. and those endorsed by the Canadian Diabetes association and the Australian Diabetes Society[15, 16].

Conclusion

Metformin is an ideal drug for treatment of type 2 diabetes. It is weight neutral and rarely if ever causes hypoglycemia as a single agent. There is a well documented cardiovascular benefit of taking metformin which has been known since the UK Prospective Diabetes Study (UKPDS). Lactic acidosis associated with metformin use is extremely rare based on the current evidence and there does not seem to be a connection between the use of metformin in the current recommended doses and lactic acidosis. Metformin use has not been studied extensively in patients with chronic kidney disease, but it has been often used in patients with mild to moderately reduced renal function without any adverse events as in the case of our patient. Failing to prescribe metformin in an appropriate population because of a theoretical fear may unnecessarily deprive patients of multiple potential benefits of this medication. In this day and age, when all are attentive to runaway medical costs, it is ironic that we have a safe, inexpensive, well-tested medical therapy that people are hesitant to use because of an unsubstantiated concern about lactic acidosis.

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