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METFORMIN IN CHRONIC KIDNEY DISEASE: TIME FOR A RETHINK

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Metformin has traditionally been regarded as contraindicated in chronic kidney disease (CKD), though guidelines in recent years have been relaxed to permit therapy if the glomerular filtration rate (GFR) is > 30 mL/min. The main problem is the perceived risk of lactic acidosis (LA). Epidemiological evidence suggests that this fear is disproportionate. Lactic acidosis is a rare complication in type 2 diabetes mellitus (T2DM), with an incidence of 6/100,000 patient-years. The risk is not increased in metformin-treated patients. Metformin possesses a number of clinical effects independent of glucose reduction, including weight loss, which are beneficial to patients. The risk of death and cardiovascular disease is reduced by about a third in non-CKD patients. Since metformin intoxication undoubtedly causes LA, and metformin is renally excreted, inappropriate dosage of metformin will increase the risk of LA. It is suggested that introduction of metformin therapy to more advanced stages of CKD may bring therapeutic benefits that outweigh the possible risks.

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It is Monday morning in the conference room. The doctor on weekend duty reports that a patient with type 2 diabetes (T2DM) and chronic kidney disease (CKD) has been admitted to the intensive care unit (ICU) with uro-sepsis, lactic acidosis (LA), and renal failure. The other doctors look at each other and sigh; if only the general practitioner had not given the patient metformin, this would not have happened. The question arises: is this almost universal reaction justified?

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THE CASE AGAINST METFORMIN

The main problem with metformin is its association with LA. Lactic acidosis is defined as an arterial lactate of > 5 mmol/L and a blood pH ≤ 7.35 (1,2). There are two forms of LA. Type A is anaerobic LA caused by lactate overproduction in order to regenerate adenosine triphosphate (ATP) in the absence of oxygen, and is usually seen in the presence of circulatory collapse, e.g. heart failure, sepsis, and shock. Type B, the aerobic version, is caused by underutilization of lactate due to impaired removal by oxidation or gluconeogenesis, and is the type seen in liver disease, diabetes, cancer, and alcohol and metformin intoxication. Combinations of Type A & B are possible.

The therapeutic trough level for metformin is 0.7 (0.3–1.0) mg/L (3) (for µmol/L, multiply by 7.75). The pragmatic upper therapeutic limit is 5 mg/L (4).

There is no doubt that metformin in toxic doses is a cause of LA. In rats, plasma lactate begins to rise if the metformin concentration is > 20 mg/L (5). Intentional metformin overdose usually leads to hyperlactemia (6), and often to LA. This can be fatal in cases with plasma metformin > 50 mg/L (7). Some cases are accompanied by a raised creatinine. Since the most common symptom of metformin intoxication is vomiting and diarrhea, it is possible that the reduced renal function is caused by prerenal dehydration and/or circulatory collapse. Metformin is renally excreted (8,9), with a clearance approximately linearly correlated to glomerular filtration rate (GFR). There are thus two situations where metformin intoxication can occur: failure to reduce the dose in the presence of CKD, and acute uremia. It is possible that a vicious cycle can develop with acute uremia causing metformin accumulation leading to vomiting, dehydration, further worsening of renal function and metformin intoxication. Thus, vomiting is both a consequence and cause of metformin intoxication.

Phenformin is a biguanide, and causes LA by inhibiting hepatic and peripheral oxidative phosphorylation, resulting in a secondary increased lactate production

by anaerobic pathways. This led to deregistration of this product, and a raised degree of suspicion for biguanide treatment in general. A series of case histories of patients with LA, who had been treated with metformin, which is also a biguanide, cemented metformin as a cause of LA, to be avoided in all patients predisposed to LA, e.g. patients with cardiac, renal or hepatic failure. The drug has since been regarded as contraindicated in patients with CKD. This restriction has been eased in recent years, such that metformin (at a reduced dose) is permitted if the GFR is > 30 mL/min, with some variation between regulatory authorities (3). One could also argue that any drug, such as metformin, that reduces hepatic gluconeogenesis, will dispose toward LA in situations where body energy requirements are high, such as sepsis. If the patient develops renal failure, the risk of subsequent metformin intoxication will compound the problem. Patients should therefore be advised to temporarily cease ongoing metformin therapy if they become ill. This is a recommendation that is independent of their renal status, and common to other drugs, such as angiotensin-converting-enzyme (ACE)-inhibitors, that are otherwise considered useful in CKD. However, the hypothesis that such a "sick day" rule would mitigate or remove the risk of metformin-associated LA (MALA) is theoretical.

THE CASE FOR METFORMIN

Several arguments can be advanced in defense of metformin as a useful drug in CKD, and are briefly summarized here.

METFORMIN IS NOT PHENFORMIN

Phenformin's lactogenic effect is 140 times greater than that of metformin (5). As a result, the incidence of MALA is approximately 5% of the risk of phenformin-associated LA (10).

METFORMIN IS A USEFUL DRUG IN T2DM

Metformin increases insulin sensitivity, reduces glucose absorption from the intestine, increases peripheral glucose uptake in cells, reduces hepatic gluconeogenesis in the liver and reduces weight, all highly desirable goals in T2DM (11). Further advantages are a reduction in blood pressure and plasma lipids, plasminogen activator inhibitor, and insulin, and an increase in fibrinolytic activity. In addition, hypoglycemia is a rare complication of treatment. Sulfonylurea and insulin both have hypoglycemia as a major and common side effect. The risk of hypoglycemia doubles in the presence of CKD (12). Metformin is the only drug demonstrated to significantly reduce the risk of mortality and myocardial infarction (in overweight patients without CKD), by 36% and 39% respectively (13), this effect being independent of glycemic control. For these reasons, metformin is the first line drug of choice in obese T2DM.

Metformin was previously contraindicated in heart failure. However, a meta-analysis of performed trials showed a significantly reduced risk for mortality and hospital admission related to metformin (14), with no risk of LA. Use of the drug in the presence of heart failure is now so common that a randomized controlled trial is no longer possible (15).

METFORMIN IS NOT USUALLY THE CAUSE OF LA

Diabetes mellitus per se disposes to hyperlactemia, the concentration of lactate being double the level of healthy controls (16), and physical exercise in untreated T2DM causes a 2.8 times increase in p-lactate, similar to metformin-treated patients (17). Ketoacidosis is commonly accompanied by LA (18). The increased LA rates seen in patients with heart failure can be related to poor circulation, and, in patients with hepatic failure, to reduced hepatic metabolism of lactate. A controlled investigation showed no increase in lactate concentration or turnover in metformin-treated patients (16).

THERE IS NO EPIDEMIOLOGICAL EVIDENCE THAT METFORMIN USE INCREASES THE RISK OF LA

A Cochrane analysis of 347 controlled studies covering 70,490 patient-years of metformin use revealed no cases of LA and no significant change in p-lactate (19). There is no correlation between metformin and lactate controls (3). In 43% of these studies, CKD was not a contraindication. In a population of T2DM patients with no access to biguanide therapy, the incidence of LA was 9.7–16.9/100,000 patient-years (20). In all cases, proximal medical causes were identified in the form of hypotension, sepsis, or congestive heart failure, and can thus be classified as Type A LA. Thus, all diabetic patients, regardless of treatment, have an increased risk of LA when faced with circulatory challenge, and the risk of MALA should be compared with this intrinsic risk. The quoted incidence of MALA varies from 0–9.7 (average 6.3) (21) and is thus comparable with this figure. Indeed, in two studies where this was investigated, the incidence of sulphonylurea-associated LA was higher than MALA (22,23). One might argue that this low incidence was the result of pedantic attention to contraindications; in reality, stated contraindications, mainly CKD, are widely

ignored in general practice, with a contraindication prevalence varying from 19–94% of treated patients (24,25). In one center over 1,000 patients with CKD have been treated without any cases of MALA (26).

METFORMIN INTOXICATION IS NOT USUALLY THE CAUSE OF MALA

Virtually all cases of MALA occur in individuals with severe conditions that in themselves cause LA. In a study of 20 MALA cases, only 7 (35%) had raised concentrations of p-metformin (27), and in another series of 47 cases of MALA, only 13 could be ascribed to metformin (28). Metformin concentration is not correlated to plasma lactate in MALA (28).

Lalau & Race (29) have suggested that, since many cases of MALA are unrelated to metformin, the term MALA should be divided into metformin-unrelated LA (MULA) and metformin-induced LA (MILA), the latter being defined by a raised metformin concentration. While MULA, being primarily caused by Type A LA, bears a very high mortality of 50%, the risk of mortality from MILA is only about 10% (27,29–31).

Accepting that metformin is sometimes a cause of MALA, the question then arises whether this contraindicates metformin in CKD. Assuming a mortality of 50%, the death rate from MALA is 3/100,000 patient-years. This is on a level with the risk of death from anaphylactic shock during penicillin therapy and compares favorably with the risk of dying in a traffic accident in the USA (11/100,000/year). The calculated corresponding figures for hypoglycemia-related death of patients treated with sulphonylurea and insulin are 43 and 77, respectively (32). The potential benefits on death and myocardial infarction mentioned above far outweigh this risk. It remains, however, to be demonstrated that these benefits also apply to the CKD population.

This issue presents a before-after study of 35 automated peritoneal dialysis (APD) patients treated with metformin for 11 months (33). The metformin dose (0.5–1.0 g/day) was relatively high, considering the patients' GFR. Thus, metformin concentrations were elevated in 81% of samples and markedly elevated (> 5 mg/L) in 4%. Hemoglobin A1C fell from 7.4 to 6.4% (57 to 46 mmol/mol) and insulin requirements fell 30%. Body mass index fell by 1.5 kg/m2 (i.e. 4–5 kg). No change in anion gap, or pH was seen, and only 0.76% of blood samples had a p-lactate above 2 mmol/L. There was no correlation between metformin concentration and lactate, and no cases of LA. These findings are in accordance with the hypothesis that metformin is effective and safe even in severe renal failure. The authors suggest that peritoneal dialysis, by causing rapid removal of lactate and restitution of acid-base balance, may in itself protect against LA. A surprising result of this study, not commented upon by the authors, was that none of the patients died; even considering the patients' young age (54 years), some 15% would be expected to have died. The findings are in accordance with a recent publication by Duong *et al*. (3), who treated 5 patients with CKD5 (of whom 2 were treated with dialysis) with 250–500 mg metformin per day without side effects, LA, altered lactate levels, or raised plasma metformin. In one hemodialysis patient, the clearance of metformin during dialysis was 149 mL/min.

CONCLUSION

As was the case with heart failure, it is time to reconsider the present contraindication for CKD patients. There is no reason to believe that the cardiovascular benefits demonstrated for otherwise healthy diabetic patients (and patients with heart failure) should not also be applicable to CKD patients, whose risk of cardiovascular disease is massively increased. In this regard, the risk of LA is negligible, and clinical worries about LA disproportionate (34). Lactic acidosis is an unpredictable and rare disease occurring in diabetic patients facing sudden circulatory challenge.

The main problem for metformin treatment in CKD patients is the prevention of intoxication. Dosage guidelines for CKD patients have recently been published (9). These recommend the following maximum daily doses related to creatinine clearance: 3 g (120 mL/min); 2 g (60 mL/min); 1 g (15 mL/min); 500 mg (15 mL/min). It would be advantageous to monitor therapy using regular metformin concentration measurements. These would, however, mainly be useful for patients who are being undertreated: the absence of over dosage in the routine situation does not preclude exacerbation of a Type A LA episode accompanied by worsening of renal function. Access to metformin concentration measurements is useful in cases admitted with LA in order to differentiate between MULA and MILA. In the absence of concentration monitoring, the metformin dose in dialysis patients should not exceed 250 mg/d in peritoneal dialysis patients, and 500 mg after each dialysis in hemodialysis patients. Initial determination of plasma lactate might be useful to identify the occasional patient with spontaneously increased lactate (3).

The physician contemplating metformin treatment in a CKD patient should also address other problems. He should be aware that prescription in CKD 4–5 is outside its licensed use and that the evidence base for this

approach is incomplete. The patient will understandably be confused by the product information, which states that the drug is contraindicated. As with any drug, the patient should be informed of the advantages, disadvantages, and putative side effects of metformin. He should be advised to temporarily cease therapy if he develops sudden weight loss or acute illness, particularly if accompanied by vomiting and diarrhea. X-ray contrast can occasionally cause acute renal insufficiency. In accordance with recent guidelines (35), patients with an estimated GFR < 45 mL/min should stop metformin 48 hours before contrast investigations, and restart 48 hours after. Other contraindications, e.g. liver disease and pregnancy, remain.

An answer to the question posed at the start of this paper might be: possibly, if the metformin dose had been inappropriate to the premorbid GFR, and/or the plasma metformin is > 5 mg/L; otherwise, probably not. The physicians might also pause to wonder whether the diabetic CKD patient in the next bed with a myocardial infarction would still have been in good health if the general practitioner had treated him with metformin.

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