

Metformin: The Safest Hypoglycaemic Agent in Chronic Kidney Disease?

Helen J. Nye^a William G. Herrington^b

^aNorth Bristol NHS Trust, Bristol, and ^bOxford Kidney Unit, Churchill Hospital, Oxford Radcliffe Hospitals NHS Trust, Oxford, UK

Key Words

Metformin · Lactic acidosis · Renal impairment

Abstract

Metformin is the first-line oral agent in the treatment of type 2 diabetes and has many established benefits, including the reduction of macrovascular complications of diabetes. Its prescription in patients with renal impairment is limited by concerns relating to the theoretical risk of lactic acidosis, a fear which is perpetuated by numerous case reports in which it is implicated. Critical review of this literature calls into question the validity of these claims, with metformin usually acting as an 'innocent bystander' in acutely unwell patients with conditions well recognised to precipitate lactic acidosis such as sepsis or hypovolaemia. In fact, the evidence supports the safe use of appropriate doses of metformin in patients with chronic stable renal impairment, and highlights the important possible greater risks of the alternatives, most notably severe hypoglycaemia in patients taking sulphonylureas and/or insulin and fluid retention in patients taking a thiazolidinedione. Other traditional contraindications to metformin use such as heart failure are also being re-evaluated, as the benefits of metformin in these patients are increasingly recognised. Physicians should weigh this evidence carefully before deciding to withdraw metformin therapy in their patients with stable chronic kidney disease.

Copyright © 2011 S. Karger AG, Basel

Introduction

Metformin is a highly effective agent in the treatment of type 2 diabetes. In addition to controlling blood sugar, it has been shown to reduce the long-term complications of diabetes, including macrovascular disease. The long-standing and now entrenched anxiety over the prescription of metformin in patients with chronic renal impairment has arisen from a theoretical risk of lactic acidosis arising from reduced clearance and consequent accumulation of the drug. However, critical analysis of the available literature suggests that the contribution of metformin to lactic acidosis is minimal, with tissue hypoxia being the most significant risk factor.

Background

Metformin is a biguanide which acts independently of insulin to lower blood glucose levels primarily through the inhibition of hepatic gluconeogenesis. It is the first-line oral agent in the treatment of type 2 diabetes mellitus, and there is growing interest in its potential in type 1 diabetes. Extensive clinical experience has been complemented by favourable results from the UK-PDS, in which metformin was shown to reduce the incidence of macrovascular complications (myocardial infarction, angina, sudden death, stroke and peripheral vascular

disease) in overweight patients with type 2 diabetes. This benefit was independent of glycaemic control and other traditional cardiovascular risk factors [1]. In contrast to the oral alternatives and insulin, metformin is not associated with a risk of hypoglycaemia, nor does it cause weight gain [2]. In addition, recent observational data suggests that, when compared to sulphonylureas and insulin, metformin is associated with a reduced risk of developing solid organ cancer (after cardiovascular disease, the second largest cause of death in patients with diabetes) [3].

Between 20 and 40% of patients with diabetes ultimately develop diabetic nephropathy. As a result of the combination of chronic kidney disease, diabetes and, in most cases, other traditional risk factors, these patients are at particularly high risk of cardiovascular events. However, in this group, prescription of metformin has been limited by a concern that its accumulation may be associated with lactic acidosis. Metformin is eliminated unchanged by the kidney, and would be expected to accumulate as the glomerular filtration rate (GFR) falls, increasing the theoretical risk of lactic acidosis. Current NICE guidelines [4] recommend that the dose of metformin should be reviewed if the serum creatinine exceeds 130 $\mu\text{mol/l}$ (or estimated GFR is $<45 \text{ ml/min/1.73 m}^2$) and that metformin should be stopped in patients in whom the creatinine rises above 150 $\mu\text{mol/l}$ or eGFR falls to $<30 \text{ ml/min/1.73 m}^2$.

Evidence from the Literature

Predictably for such a rare event, the evidence for metformin-associated lactic acidosis is derived mainly from case reports or physician reports to drug safety committees. While metformin overdose can certainly cause lactic acidosis, analysis of all case reports has repeatedly undermined the notion of a simple causal relationship between metformin use and lactic acidosis in patients with diabetes [5, 6]. Particular criticisms have included: inadequate, or poor quality of information in reports, failure to measure metformin concentrations, and a normal metformin concentration at the time of lactic acidosis. In the majority of cases, other insults including sepsis, hypovolaemia, ischaemic events or hepatic failure are the prime cause of the lactic acidosis, with metformin merely an 'innocent bystander'.

The conclusion of the most recent Cochrane review [7] is clear: there is no evidence from prospective comparative trials or from observational cohort studies that met-

formin is associated with an increased risk of lactic acidosis, or with increased levels of lactate, compared with other oral hypoglycaemic treatments. Pooled data from 347 comparative trials and cohort studies revealed no cases of fatal or non-fatal lactic acidosis in 70,490 patient-years of metformin use or in 55,451 patient-years in the non-metformin group. This implies an upper limit for true incidence of lactic acidosis of 5 per 100,000 patient-years. Although individual creatinine concentrations were not available in the meta-analysis, 45% of the studies reviewed did not exclude patients with a creatinine $>133 \mu\text{mol/l}$. This equates to 37,360 patient-years of metformin use in studies including chronic kidney disease patients with no episodes of lactic acidosis.

A recent nested case-control study using the UK-based General Practice Research Database (GPRD) identified over 50,000 patients with type 2 diabetes taking oral anti-diabetes drugs with or without concomitant insulin use [8]. All cases of lactic acidosis occurring after first prescription of an oral anti-diabetic drug were reviewed. The crude incidence rate of lactic acidosis was calculated as ~ 3.3 per 100,000 patient-years in metformin users, and ~ 4.8 per 100,000 patient-years in sulphonylurea users. The incidence of lactic acidosis in patients with diabetes does not appear to be influenced by the use of metformin.

This study also investigated the incidence of hypoglycaemia presenting to a physician within the same patient population. It revealed that the crude incidence of hypoglycaemia for those patients prescribed sulphonylureas was 110 per 100,000 patient-years and for metformin users (usually prescribed in combination with other hypoglycaemic agents) 60 per 100,000 patient-years. Of the 73 cases of severe hypoglycaemia (3.6% of the total events) that resulted in hospitalisation or death, only 3 patients were on metformin alone. Compared to patients taking metformin alone the adjusted odds ratios for severe hypoglycaemia with sulphonylureas, insulin and the two in combination were 2.8, 16.5 and 39.9, respectively. Renal failure was the only co-morbidity that was significantly associated with an increased risk of hypoglycaemia. It has therefore been suggested that the risk of death as a result of sulphonylurea- (or insulin-) induced hypoglycaemia in CKD patients is likely to be greater than the risk of death due to metformin-associated lactic acidosis.

Metformin has other potential advantages: a recent letter from a nephrologist in India [9], where in the year 2000 there were 31.7 million people with diabetes, expands on the particular advantages of metformin over

insulin therapy in the developing world. Metformin is much cheaper than insulin, and avoids the infection risk associated with subcutaneous injections and invasive glucose monitoring.

The stated contraindications to metformin include: hypoxic conditions (respiratory failure and heart failure), impaired lactate clearance (liver failure) and impaired metformin clearance (renal failure). However, the degree of impairment (of any organ) that should preclude metformin use has not been well-defined. Indeed, in a meta-analysis of retrospective cohort studies of patients with both diabetes mellitus and heart failure (once believed to be a contraindication to metformin use), metformin was associated with reduced rates of hospitalisation and death and was the only anti-diabetic drug that emerged without evidence of any associated harm. In contrast, thiazolidinediones cause fluid retention and are associated with an increased risk of hospitalisation with symptomatic heart failure [10]. Rosiglitazone is also associated with an increased risk of cardiovascular events. It has recently been suspended by European drug regulatory agencies, and in the USA new FDA restrictions advise its prescription only in patients whose diabetes cannot be controlled on other medications. Thiazolidinediones are thus unlikely to benefit diabetic patients with a reduced GFR who already have both impaired handling of salt and water and a higher baseline risk of cardiovascular events.

Pharmacokinetic studies of metformin are in small numbers of subjects, and suggest that metformin doses should be reduced by one third in patients with eGFRs of <45 ml/min/1.73 m² [11]. Metformin is likely to be tolerated at eGFRs of <30 ml/min/1.73 m², particularly in patients with stable CKD with no other significant hepatic or respiratory failure. However, more detailed pharmacokinetic investigation of metformin elimination in renal patients is required before current dosing guidelines can be changed. Metformin is removed by haemodialysis, but unlike drugs such as vancomycin, gentamicin and digoxin, plasma concentrations are not available in routine clinical practice. Increasing the availability of metformin assays would not only serve to reassure physicians that reducing metformin doses in renal impairment was safe and sufficient to preclude accumulation, but careful monitoring might even allow metformin to be administered three times weekly post-dialysis in patients with end-stage renal disease.

Conclusions

Lactic acidosis is rare and unpredictable. It is usually precipitated by an additional acute condition predisposing to tissue hypoxia. Metformin is an effective oral agent in the treatment of type 2 diabetes and in the prevention of its complications, particularly in overweight patients. Although a number of reports have been published suggesting that metformin is a cause of lactic acidosis, systematic review of all the available trials and cohort studies does not support this. In fact, the evidence suggests that type 2 diabetes mellitus itself may be associated with reduced lactate clearance and be a more important risk factor for lactic acidosis than metformin.

Sulphonylureas, the major oral alternative, and of course insulin, are associated with weight gain and hypoglycaemia (which is also more common in patients with renal impairment). They carry a more significant total morbidity and mortality than lactic acidosis. In spite of this, the majority of patients with chronic stable kidney disease (who stand to gain most from its cardiovascular benefits) are being denied metformin.

Metformin will always be avoided in patients whose renal function is deteriorating acutely and in those patients in whom oxygenation, tissue perfusion or liver function are severely compromised. However, in patients with type 2 diabetes and stable chronic kidney disease, clinicians are doing their patients a disservice by prematurely and unnecessarily withdrawing metformin treatment.

Acknowledgement

Thanks to Dr. C.G. Winearls for his review of the manuscript.

Conflicts of Interest

None to declare.

References

- 1 UK Prospective Diabetes Study (UKPDS) Group: Effect of intensive blood glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;352:854–856.
- 2 Bolen S, Feldman L, Vassy J, Wilson L, Yeh HC, Marinopoulos S, Wiley C, Selvin E, Wilson R, Bass EB, Brancati FL: Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. *Ann Intern Med* 2007;147:386–399.

- 3 Currie CJ, Poole CD, Gale EA: The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. *Diabetologia* 2009;52: 1766–1777.
- 4 NICE Clinical Guideline CG87 (May 2009): Type 2 diabetes – newer agents (a partial update of CG66).
- 5 Stades AM, Heikens JT, Erkelens DW, Holleman F, Hoekstra JB: Metformin and lactic acidosis: cause or coincidence? A review of case reports. *J Intern Med* 2004;255:179–187.
- 6 Lalau JD, Race JM: Lactic acidosis and metformin therapy: searching for a link with metformin in reports of ‘metformin-associated lactic acidosis’. *Diabetes Obes Metab* 2001;3:195–201.
- 7 Salpeter SR, Greyber E, Pasternak GA, Salpeter EE: Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes. *Cochrane Database Syst Rev* 2010;4: CD002967.
- 8 Bodmer M, Meier C, Krähenbühl S, Jick SS, Meier CR: Metformin, sulfonylureas, or other antidiabetes drugs and the risk of lactic acidosis or hypoglycaemia. *Diabetes Care* 2008;31:2086–2091.
- 9 Mani MK: Metformin in renal failure – weigh the evidence. *Nephrol Dial Transplant* 2009;24:2287–2288.
- 10 Eurich DT, McAlister FA, Blackburn DF, Majumdar SR, Tsuyuki RT, Varney J, Johnson JA: Benefits and harms of antidiabetic agents in patients with diabetes and heart failure: systematic review. *BMJ* 2007;335: 497–506.
- 11 Sambol NC, Chiang J, Lin ET, Goodman AM, Liu CY, Benet LZ, Cogan MG: Kidney function and age are both predictors of pharmacokinetics of metformin. *J Clin Pharmacol* 1995;35:1094–1102.