Metformin: safety in cardiac patients

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ABSTRACT

Metformin is a biguanide, insulin sensitiser that reduces blood sugar levels. There are concerns about the risk of lactic acidosis in patients receiving metformin who have procedures requiring iodinated contrast, and in those with renal impairment or heart failure. The data on which these concerns are based are reviewed, with the conclusion that metformin treatment is rarely to blame for lactic acidosis. A generic policy of stopping metformin 48 h before and 48 h after the procedure in all patients is counterintuitive, lacks any evidence base and does not conform to the principles of best practice. In patients with heart failure, although the underlying condition can predispose to lactic acidosis, existing evidence suggests that metformin use is associated with improved outcome rather than increased risk.

Metformin is a biguanide, insulin sensitiser that also reduces hepatic gluconeogenesis, thereby reducing blood sugar levels. It can be used in combination with every other oral antidiabetic agent and also insulin. It has a short half-life, about 6 h, with 90% being eliminated by renal excretion within 24 h. Metformin has inherited a legacy of concern from phenformin, its biguanide predecessor, which was shown to have a strong causal association with lactic acidosis (LA) and therefore withdrawn from clinical practice in 1978.[1]

There is a widely held clinical impression that metformin causes LA in patients with diabetes or renal dysfunction. Thus its use in cardiac patients having intravenous or intra-arterial contrast, and in patients with heart failure, has been questioned. Many cardiac catheterisation laboratory protocols stipulate withholding metformin for both 48 h before and 48 h after any planned diagnostic or interventional procedure. Patients who have not stopped their metformin often have their procedure delayed, with considerable repercussions on service delivery.

Metformin is not nephrotoxic and there is no known reaction between metformin and iodinated contrast media; the policy of withdrawal is linked to a theoretical risk of developing LA in patients predisposed to acute deterioration in their renal function after contrast administration. There is thus the potential for metformin accumulation which could lead to increased serum lactate levels. *Is this concern justified*?

THE RISK OF STOPPING

Hyperglycaemia itself may be harmful during high-risk coronary and carotid interventions.[2 3] No specific study has examined the longer-term impact for the elective and stable patient after temporary cessation of metformin treatment with respect to the "rebound hyperglycaemia". However, the effect of a 1–2 week metformin "washout" was explored in a patient subset within the Diabetes Prevention Program, which randomly assigned 3234 people with impaired glucose tolerance to placebo, metformin or a lifestyle-modification programme for a mean 2.8 year follow-up.[4 5] The odds of diabetes onset (defined by an impaired oral glucose tolerance test) increased by 50% in the metformin group compared with the placebo group during the washout period but the difference did not reach statistical significance ($p = 0.098$).

THE RISKS OF CONTINUING

LA occurs in non-diabetic patients in association with infection, cancer, liver failure and renal failure and is invariably fatal unless the underlying condition is corrected. Box 1 shows a list of predisposing risk factors for the development of LA.

Metformin was introduced to the USA in May 1995 and over the subsequent 12 months the FDA received reports of LA in 66 patients treated with metformin. In 47 patients, the diagnosis was confirmed on the basis of circulating lactate values (>5 mmol/l), in accordance with established criteria for the diagnosis of LA.[6] Of these 47 patients, 43 had one or more risk factor for LA; 30 had pre-existing cardiac disease, of whom 18 had histories of congestive heart failure and 13 patients had pre-existing renal insufficiency, including two patients undergoing dialysis. Three patients had chronic pulmonary disease with hypoxia and eight patients were over the age of 80 years. Only four patients had no apparent risk factors when treatment with metformin was initiated, and all four recovered. Since then, the association between metformin and LA has provoked considerable controversy, relying necessarily on anecdotal reports, with the incidence currently estimated at 2–5 cases per 100 000 patient years.[7]

In patients with type 2 diabetes, the reported incidence of LA is similar in patients who are taking metformin and in those who have never taken it, when risk factors for LA have been excluded.[8] Mortality in patients with metformin-attributed LA seems to be ~40% and also seems to be associated with heart failure. In the majority of reported cases, it was felt that metformin was not the initial cause of the LA, but it might have contributed to the severity of the acidosis. The causal mechanism of LA is complex but is thought to result from a shift in intracellular redox potential from aerobic to anaerobic metabolism, leading to increased cellular lactate production.[9]

An interesting retrospective study evaluated metformin prescribing habits to determine whether they were in accord with published contraindications and precautions.[10] This showed

Box 1 Risk factors for the development of lactic acidosis are similar, irrespective of diabetic status

- Age >80 years
- Tissue hypoxia
  - Decreased cardiac output
  - Respiratory failure
- Hepatic function impairment
- Renal impairment
- Sepsis
- Surgery
- Ethanol intoxication
- Diabetic ketoacidosis
- Fasting/malnutrition
- Short bowel syndrome (jejunoileal bypasses, small bowel resection)
- Anti-retroviral treatment
- High doses (deliberate overdose) of metformin >2 g/day

that doctors (probably having recognised this low tendency for LA) rarely stick to guidelines rigorously and patients were treated with metformin despite having clinical conditions that theoretically placed them at risk for developing LA. Despite this "misuse", no cases of LA were seen. In another similar study from Scotland involving 1847 patients taking metformin, the prescription was for non-guideline use in 24.5% patients and despite this, only one case of LA occurred over a 30 month follow-up in a person who succumbed to heart failure.[11]

METFORMIN AND HEART FAILURE

Diabetes is a common comorbidity in patients with heart failure and portends a worse prognosis.[12] Metformin is "contraindicated" in heart failure because of the theoretical concern of precipitating LA, even though long-term outcome trials have not been performed. On the contrary, there are substantial data from the heart failure literature which corroborate the safety of metformin. Large retrospective registry analyses suggest that, paradoxically, metformin is the only antidiabetic drug which has been shown to confer morbidity (reduction in repeat hospitalisation for heart failure), and mortality benefit for this clinical setting, including in the elderly.[13 14] Similarly, no cases of LA were reported in these cohorts.

A theoretical reason for benefit has been suggested. In a murine model of heart failure, the cardioprotective mechanisms of metformin were shown to be independent of its hypoglycaemic effect and mediated by chronic activation of AMP-activated protein kinase (AMPK).[15]

A pilot study to evaluate the feasibility of undertaking a large randomised controlled trial with clinical end points to assess metformin safety in heart failure was recently undertaken, with randomisation planned to either 1500 mg of metformin daily or matching placebo for 6 months.[16] Patient recruitment proved futile with all 58 screened patients being excluded. The main reasons for exclusion were use of insulin treatment, glycosylated haemoglobin <7% and pre-existing use of high-dose metformin, leading to the pilot trial being abandoned and leaving prospects of a future trial equally barren. Accordingly, many question the validity of metformin's "contraindicated" status for treating diabetic cardiomyopathy, on the basis of an outdated and evidence-deficient suspicion of causing LA.[17 18]

THE EVIDENCE FOR SAFETY

To help allay concerns about the safety of metformin, Bristol-Myers Squibb (New York, USA) commissioned a large study (the Comparative Outcomes Study of Metformin Intervention Versus Conventional Approach (COSMIC)), comparing 1 year of treatment with metformin with "usual care" with other antidiabetic agents. The results showed no differences in safety outcomes between the 7227 patients who received metformin and the 1505 patients who received usual care. There were no cases of LA in either group.[19]

Two large industry-independent studies have provided an impressive body of evidence to support the safety and effectiveness of metformin. First, the landmark UK Prospective Diabetes Study (UKPDS) randomised a 753 patient subset who were overweight to either a conventional strategy, comprising diet alone (n = 342) or to intensive glycaemic control with metformin (n = 411). Metformin demonstrated better efficacy in reducing diabetes-related end points, including macrovascular disease, with no compromise in safety, either in this randomised cohort or the overall UKPDS trial population (n = 4075) over a median 10.7 year follow-up.[20] Metformin also encourages weight loss, which is of proven cardiovascular benefit in diabetic and obese patients.[21] This safety record and efficacy of metformin was corroborated the Diabetes Prevention Program (n = 2155),[5] which showed that it reduced the risk of diabetes onset by 31% compared with placebo.

The recently published Cochrane Review meta-analysed the incidence of fatal and non-fatal LA with metformin use compared with placebo and other glucose-lowering treatments in patients with type 2 diabetes mellitus.[8] Pooled data from 206 comparative trials and cohort studies showed no cases of fatal or non-fatal LA in 47 846 patient-years of metformin use or in 38 221 patients-years in the non-metformin group. It was concluded that there is no evidence from prospective comparative trials or from observational cohort studies that metformin is associated with an increased risk of LA.

Despite the findings from controlled trials, registries and meta-analyses, concerns about the risk of metformin-related LA are perpetuated by case reports and feature in guidelines issued by the major professional associations (table 1).

A recent review of the case reports concluded that the vast majority of metformin-associated LA, particularly fatal cases, are related to comorbidity or the coincidence that diabetic patients are prone to develop serious medical conditions that lead to LA, rather than to the metformin itself.[22] Another review of all reported cases occurring after intravenous contrast administration emphasised pre-existing poor renal function or another contraindication to metformin usage.[23] The lack of correlation between lactate levels and metformin levels in these patients suggests that metformin is an innocent bystander.[24] In these cases, the need for contrast administration needs to be reviewed, and aggressive hydration used to minimise the risk of contrast-induced nephropathy.

CONCLUSION

Actual numbers of documented cases of metformin-associated LA are extremely small when considering its wide usage. A causal link is tenuous and is derived from cases of metformin overdose. In patients with heart failure, although the underlying condition can predispose to LA, existing evidence suggests that metformin use is associated with improved outcome rather than increased risk. The accumulation of metformin in the setting of renal insufficiency might be expected to precipitate LA in some patients who are at risk—for example, older patients and those

Table 1 Summary of guideline statements on metformin use in procedures requiring intravenous contrast administration

Professional body	Metformin advice
NICE[25]	Should be withdrawn if serum creatinine is ⩾150 μmol/l, if the hepatic function is deranged or if any cause of tissue hypoxia is likely
ACC/AHA/SCAI[26]	Whenever possible, metformin (especially in those with pre-existing renal dysfunction) should be withheld for 24 h before performing PCI and for 48 h afterwards*
American Diabetes Association[27]	Discontinue for 48 h after contrast dye procedures. Contraindicated if serum creatinine is > 1.5 mg/dl in men or >1.4 mg/dl women
Royal College of Radiologists[28]	► If serum creatinine is normal, and a low volume of contrast agent (⩽100 ml) is to be administered intravenously, no special precaution is required ► If serum creatinine is normal, but ⩾100 ml of contrast agent or the intra-arterial route is to be used, metformin should be withheld for 48 h after the procedure ► If the serum creatinine is raised, the need for the contrast agent should be reassessed. If contrast injection is deemed necessary, metformin should be withheld for 48 h before and 48 h after the contrast is given and the renal function reassessed before restarting the metformin treatment
Suggested recommendation	*For use of Contrast:* ► If the serum creatinine is normal, no need to withdraw ► If the serum creatinine is raised >150 μmol/l (or 1.5 mg/dl): – Contrast <100 ml—no need to withdraw – Contrast >100 ml—withdraw for 48 h before and 48 h after the contrast is given and reassess the renal function before restarting metformin *When contrast is not used:* ► Withdraw if creatinine >150 μmol/l (or 1.5 mg/dl) ► No need to withdraw in patients with heart failure

No guideline has been published from the Joint British Societies (JBS) or British Cardiovascular Intervention Society (BCIS) on metformin use in cardiac catheterisation procedures.
*No accompanying level of evidence category.

receiving high doses of metformin ⩾2 g/day. The risk of metformin-associated LA in patients undergoing cardiac catheterisation has not been determined, with no published trial or registry data. A generic policy of stopping metformin 48 h before and 48 h after the procedure in all patients is counter-intuitive, lacks any evidence base and does not conform to the principles of best practice. Even in those with renal impairment, the data to support a causal relationship with LA are weak. A pragmatic approach to metformin is suggested.

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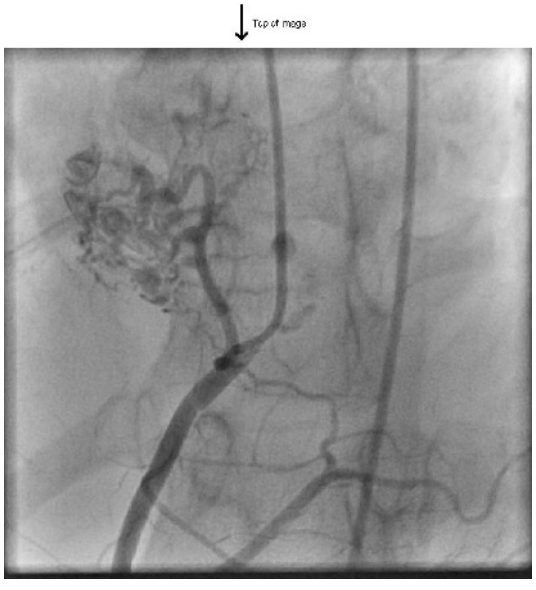
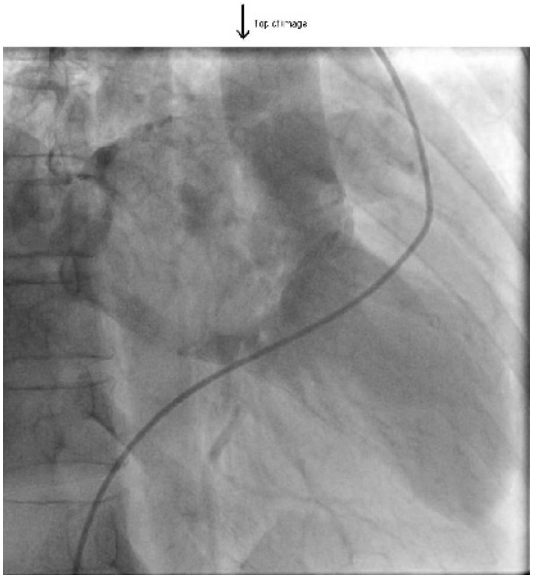
Images in cardiology

An unusual finding at cardiac catheterisation

A 61-year-old woman presented to her local hospital complaining of chest pain and shortness of breath. She was transferred to our centre at the weekend for further assessment. At coronary angiography, a complex vascular network supplied by an atrial branch of the right coronary artery was observed (see panel A and fig 1 available online only). Pulmonary angiography with follow-through revealed a large filling defect in the left atrium, which partly prolapsed into the left ventricle in diastole (see panel B and fig 2 available online only). A subsequent transoesophageal echocardiogram confirmed a large atrial mass attached to the interatrial septum. The patient underwent surgery, in which a 7.2 × 7 × 4.5 cm tumour attached to the interatrial septum was resected. Histology confirmed the diagnosis of a large left atrial myxoma. The patient made a full recovery and was discharged home 8 days later.



Panel A



Panel B

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► Additional video information in figs 1 and 2 is published online only at http://heart.bmj.com/content/vol96/issue2

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