Clinical pharmacology

Metformin and lactic acidosis

Metformin is an important agent in the management of type 2 diabetes. It 'sensitises' the body to the effects of insulin and achieves plasma glucose reduction despite lowering fasting plasma insulin concentrations. It decreases gluconeogenesis and increases the peripheral utilisation of glucose. It has an added advantage of not causing weight gain seen with sulphonylurea and insulin therapy.

Metformin has been shown to decrease the complications and mortality in type 2 overweight diabetics in the UK Prospective Diabetes Study (UKPDS). The group treated with metformin had 36% lower all-cause mortality than the group assigned diet and exercise alone.

Despite the recognised benefits of metformin therapy, there remains concern about lactic acidosis. It is a feared complication of metformin therapy and has a mortality of 50%. Consequently, the list of contraindications to metformin therapy includes many conditions believed to increase the risk of lactic acidosis. There is concern that clinicians may be denying patients the benefits of metformin therapy based on the negative reputation of phenformin, a biguanide discontinued in 1977 because of its association with unpredictable lactic acidosis and poor efficacy data.

What is metformin?

Metformin and phenformin are biguanides. While the drugs belong to the same class, there are important differences in their molecular structure. Metformin has non-polar hydrophobic side-chains substituted with two methyl groups and is therefore less lipophilic than phenformin. Consequently it has lower affinity for mitochondrial membranes.

Phenformin is metabolised in the liver while metformin is renally excreted as active drug. These differences are important when one examines the pathogenesis of lactic acidosis.

Lactic acidosis

Lactic acidosis is a biochemical disturbance in which, as a result of high serum lactate concentration, the arterial blood pH is low or may be normal due to compensatory mechanisms. Lactic acidosis is caused by increased lactate production or impaired lactate utilisation.

An arterial blood gas will reveal an increased anion gap metabolic acidosis.

Lactic acidosis can be divided into 2 types – A and B. In type A, signs of poor tissue perfusion with or without hypoxia are early and prominent. This is the most common form and may be caused by exercise, shock, severe hypoxia or may occur after convulsions. Haemorrhagic and cardiogenic shock are examples of conditions that cause type A lactic acidosis. The major problem in this condition is excessive lactate generation by peripheral tissues, due to hypoperfusion.

The biguanides cause type B lactic acidosis where signs of tissue hypoperfusion and hypoxaemia occur late. Severe liver disease, thiamine deficiency and ethanol intoxication are associated with type B lactic acidosis.

Diabetic patients are at increased risk of lactic acidosis, even in the absence of biguanide therapy. One explanation for this phenomenon is that they are prone to microvascular disease. Liver disease, renal impairment, bacterial infections, pancreatitis and haematological malignancies are associated with an increased risk.

The initial signs and symptoms of biguanide-induced lactic acidosis are difficult to distinguish from the common side-effects of this class of drugs. They include abdominal discomfort, diarrhoea, anorexia and nausea, which may progress to hyperventilation and eventual coma. Hypothermia and arrhythmias may occur, while shock and hypoxia are late events.

How does metformin cause lactic acidosis?

- Metformin is thought to impair the hepatic metabolism of lactic acid by blocking gluconeogenesis. Gluconeogenesis is the conversion of non-glucose molecules, including lactate, to glucose. Up to 70% of total daily lactate produced is taken up by the liver.
- In high doses the biguanides inhibit the oxidation of carbohydrate substrates by impairing mitochondrial function. Anoxidative carbohydrate metabolism stimulates the production of lactate.

Table I lists possible risk factors for the development of metformin-induced lactic acidosis.

Does metformin cause lactic acidosis?

This question has been raised by authors in recent years; however, it would seem that the conclusion from this debate is that the incidence of metformin-induced lactic acidosis is very low.

The true incidence is difficult to determine as there are over 300 case reports of lactic acidosis presumed to be caused by metformin, but it is difficult to quantify the total number of people exposed to the drug, i.e. the denominator.

Table I. Possible risk factors for the development of metformin-induced lactic acidosis

Risk factor	Proposed mechanism
Renal impairment Hepatitis and hepatic cirrhosis	Increased metformin serum concentrations Additive impairment of hepatic metabolism of lactate
Cardiac and pulmonary insufficiency Peripheral vascular disease	Increased risk of tissue hypoxia and lactate production
Investigation with iodinated contrast media	Transient deterioration in renal function
Concurrent use of ACE inhibitors, thiazide diuretics, NSAIDs, furosemide, nifedipine, amiloride, trimethoprim and digoxin	Competition with metformin for *renal* tubular secretion and resultant increase in serum metformin concentrations
Advanced age	Age-related decline in glomerular filtration rate

A further problem is that many of the patients in whom this complication has been reported were severely ill and had associated renal dysfunction. It is difficult to decide whether the underlying illness caused the lactic acidosis, or whether the elevated lactate due to metformin was responsible for the clinical condition.

Diabetics are predisposed to lactic acidosis. The finding of elevated metformin concentrations in some of these patients may be incidental to severe underlying illness with renal impairment.

A consistent finding in many of these case reports is that renal impairment is the one factor most strongly associated with this complication.

A catalyst for the ongoing controversy was the publication of a 2006 Cochrane Review in which the authors attempted to quantify the risk of metformin-associated lactic acidosis. A rigorous search of all prospective studies in which metformin was used for longer than 1 month was undertaken. A total of 30 294 participants were exposed to metformin with 47 486 patient years of follow-up. Many of the studies patients involved comparisons of newer drugs and thus were likely to report severe adverse effects of metformin.

No single case of lactic acidosis was found in these studies. A secondary endpoint was elevation of blood lactate levels with metformin where these levels were measured. There was no significant difference between the metformin and non-metformin groups.

Obviously risk factors for lactic acidosis could not be analysed, but it is interesting to note that many studies did not include, as exclusion criteria, the usual contraindications to metformin.

In 46% of studies impaired renal function was not an exclusion criterion and 96% of studies allowed the possibility of including patients with at least one traditional contraindication to metformin.

In a 2002 study 393 patients with contraindications to metformin were identified. All participants had a serum creatinine of 130 – 220 mmol/l, 94 had congestive cardiac failure with class III or IV symptoms, and 91 had COPD. They were randomised to discontinuing the drug or continuing the metformin. There were no cases of lactic acidosis and no difference in the mean lactate levels between the two groups.

Management of lactic acidosis

The first step is the recognition of the disorder. The diagnosis is easily missed because patients may present with nonspecific symptoms common to metformin.

Haemodialysis is the only effective treatment. Dialysis is able to remove both lactate and metformin, but often needs to be repeated as metformin in the tissues is able to stimulate lactate production.

Ventilatory and circulatory support are important components of management.

The use of sodium bicarbonate does not improve survival. It may result in hypernatraemia and fluid overload. Alkali-induced stimulation of lactic acidosis may occur.

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In a nutshell

- Metformin-associated lactic acidosis is extremely rare.
- Prospective studies have so far failed to demonstrate that the traditional contraindications increase the risk of this life-threatening complication.
- Case reports have suggested that renal dysfunction may be the strongest association with this disorder.
- A creatinine level greater than 130 mmol/ l in men and 120 mmol/ l in women has been suggested as a contraindication, but an estimation of the creatinine clearance is more meaningful.