ARTICLE

Safe prescribing of metformin in diabetes

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SUMMARY

Metformin is the first-line pharmacological therapy for type 2 diabetes. It is the only glucose-lowering oral drug that has been shown to reduce mortality in patients with diabetes.

The most common adverse effect is gastrointestinal upset. Starting at a low dose and increasing it slowly reduces this risk. Taking metformin with food also helps.

Numerous contraindications to the use of metformin are listed in the product information, including reduced renal function. Strict adherence to these recommendations may deny a valuable drug to many patients.

Introduction

Metformin lowers both fasting and postprandial blood glucose. It reduces hepatic glucose output[1] and increases peripheral glucose uptake, and may delay intestinal glucose absorption. Its use is not associated with weight gain and hypoglycaemia is extremely rare when metformin is used on its own. It lowers triglyceride concentrations and has small but beneficial effects on total and high-density lipoprotein cholesterol.

Pharmacokinetics

Metformin is absorbed throughout the gastrointestinal tract with an oral bioavailability of 50–60%. It is extensively distributed to the tissues. Metformin does not significantly bind to plasma proteins and reaches a steady state in 24–48 hours. The plasma half-life is around 3.5 hours. Metformin does not undergo hepatic metabolism and over 90% of the drug is excreted unchanged in the urine.

Clinical use

In the UK Prospective Diabetes Study metformin reduced diabetes-related and all-cause mortality, and reduced the risk of myocardial infarction in obese patients with type 2 diabetes when used as first-line therapy. It also reduced the risk of microvascular complications, but was no more effective than insulin or sulfonylureas.[2] A retrospective cohort study from the USA found a lower rate of hospitalisations for myocardial infarction and stroke and a reduced death rate when metformin was used first-line in type 2 diabetes in comparison with a sulfonylurea.[3]

Metformin is effective when used with other glucose-lowering drugs. A standard-release (3000 mg/day maximum dose) and an extended-release preparation of metformin (2000 mg/day maximum dose) are available. The extended-release preparation can be taken once daily.

Contraindications and cautions

As our knowledge of metformin has improved, many cautions have become outdated. Proposed changes to the current contraindications are shown in the Table. According to the product information, metformin is contraindicated in patients with a creatinine clearance less than 60 mL/min, moderate–severe heart failure, acute myocardial infarction, and those undergoing major surgery.

The level of renal function at which metformin becomes unsafe is not clear. Many prescribers use metformin in patients with impaired renal function. A creatinine clearance of 30 mL/min may be an appropriate level at which to consider stopping the drug, although some patients may tolerate small doses with less renal function. Patients with impaired renal function should suspend metformin if they develop vomiting, febrile illness, diarrhoea or poor tissue perfusion. There is no place for routinely measuring serum lactate to determine the safety of metformin as this does not predict those at risk of lactic acidosis.[4]

Evidence suggests that, if anything, metformin may be beneficial in people with heart failure.[5] The degree of heart failure may not predict the likelihood of benefit. Metformin should not be prescribed in those with symptomatic heart failure at rest or with minimal

From the Editor

Two new drugs for diabetes appear in this issue of *Australian Prescriber*. One of them is an inhibitor of the sodium-glucose co-transporter. Tilenka Thynne and Matt Doogue explain how this class of drugs works, and Timothy Davis discusses where the drugs may fit in the treatment of type 2 diabetes. According to Peter Davoren, metformin remains first-line therapy.

One of the adverse effects of inhibiting the sodium-glucose co-transporter is infection in the urinary tract. Thomas Jarvis, Lewis Chan and Thomas Gottlieb advise on how to treat lower urinary tract infections in adults.

Bladder dysfunction can result in incontinence. Shannon Kim, Shuo Liu and Vincent Tse say how this can be managed.

exertion where the goals of glucose control are different from those of more mobile patients.

Patients with otherwise reasonable overall health can probably take metformin in the presence of renal disease, heart disease or other underlying comorbid conditions. The metformin dose can be reduced depending on the severity of the comorbid conditions and patients should be advised to suspend the drug if they develop any acute illness predisposing them to dehydration or poor tissue perfusion.

The use of metformin around the time of surgery and other acute illnesses requiring hospital admission should be determined by the presence or risk of renal dysfunction or an infection. Metformin may need to be suspended temporarily.

Pregnancy

Despite metformin being a category C drug in pregnancy, data are reassuring in terms of the risk of congenital anomalies.[6,7] The product information recommends that metformin be replaced with insulin. However, data do not support this.

Hyperglycaemia is a recognised teratogen and stopping metformin when pregnancy is discovered (with or without the introduction of insulin) often results in significant hyperglycaemia, a state more dangerous than continuing the metformin. Metformin can be continued while adjusting the insulin dose. Many diabetes physicians continue metformin throughout pregnancy, only stopping the drug if pre-eclampsia develops.

Gestational diabetes

A large randomised trial has demonstrated that metformin is a valid alternative to insulin in gestational diabetes. Perinatal outcomes were similar, although the trial was not powered to detect differences in perinatal mortality.[8]

Lactation

The product information does not recommend metformin during lactation. However, as in pregnancy, the available data do not support withholding metformin in breastfeeding women.

Infants receive approximately a 0.2% weight-adjusted dose of metformin if the mother is breastfeeding. The concentration of metformin in breast milk is probably relatively constant and so timing doses after breastfeeding probably does not alter exposure.[9]

Gastrointestinal adverse effects

Nausea, vomiting, abdominal bloating, diarrhoea, anorexia and abdominal pain are the most common

Table **Proposed changes to product information for metformin**

Current information in product information	Proposed change
Contraindications	
Renal failure or renal dysfunction (creatinine clearance <60 mL/min)	Reduce dose for creatinine clearance 30–60 mL/min Use with caution and close supervision if creatinine clearance <30 mL/min in selected patients
Acute conditions with the potential to alter renal function, such as dehydration, severe infection, shock, intravascular administration of iodinated contrast media	Suspend metformin during acute conditions with the potential to alter renal function, including dehydration, severe infection, shock, intravascular administration of iodinated contrast media (>100 mL contrast in patients with normal renal function) until patient's condition is stable
Acute or chronic disease which may cause tissue hypoxia, such as cardiac failure, recent myocardial infarction, respiratory failure, pulmonary embolism, shock, acute significant blood loss, sepsis, gangrene, pancreatitis	Suspend metformin during acute diseases which may cause tissue hypoxia, pulmonary embolism, shock, acute significant blood loss, sepsis, gangrene or pancreatitis until patient's condition is stable Cardiac failure and chronic respiratory failure should be removed as contraindications
Elective major surgery	Can be continued perioperatively if renal function stable Suspend if acute complications
Cautions	
Lactation	Safe to use
Pregnancy (Category C) When the patient plans to become pregnant and during pregnancy, diabetes should not be treated with metformin but insulin should be used to maintain blood glucose levels as close to normal as possible, to lower the risk of fetal malformations associated with abnormal blood glucose levels	Fetal malformations associated with abnormal blood glucose levels are best prevented by good blood glucose control. If metformin is the best drug to achieve control it can be used. Abruptly stopping metformin when pregnancy is discovered can result in sudden deterioration in blood glucose control.

adverse effects of metformin. Symptoms are often self-limiting, but are persistent in some patients.

Metformin should be commenced at a low dose (500 mg/day) and always with food, to reduce the risk of gastrointestinal adverse effects. The dose should be escalated slowly. It is not uncommon for a patient who has tolerated metformin for many years to develop gastrointestinal adverse effects. It is appropriate to stop metformin in any patient who develops gastrointestinal upset to determine if metformin is the culprit. In a retrospective study, gastrointestinal effects were half as likely to occur with extended-release metformin compared with standard metformin.[10]

metformin should be taken with food to reduce gastrointestinal adverse effects

Vitamin B_{12} malabsorption

Metformin causes vitamin B_{12} malabsorption in some patients. In a placebo-controlled trial, vitamin B_{12} concentrations below the reference range were observed in 18.2% of patients taking metformin and vitamin B_{12} deficiency was seen in almost 10% (after four years). This was considerably higher than in the control group.[11] It is prudent to measure vitamin B_{12} yearly in patients taking metformin, and prescribe vitamin B_{12} if concentrations are below the reference range.

Lactic acidosis

Lactic acidosis is an adaptive physiologic response by the body to energy failure, so that cells may survive. When individuals develop conditions resulting in reduced tissue perfusion and hypoxaemia, lactate will be produced and acidosis will occur as part of the body's compensatory response.

Metformin is plagued by its association with the similar drug phenformin, which was withdrawn from the market many years ago because of its association with lactic acidosis.[12] Phenformin is thought to reduce peripheral glucose oxidation and therefore increase circulating lactate. This is not observed with metformin.[13] In a Cochrane review, the estimated upper limit for the incidence of lactic acidosis in metformin users was 4.3 cases per 100 000 patient-years compared with 5.4 cases per 100 000 patient-years in those assigned to other treatment groups.[14]

Many publications indicate that metformin is frequently prescribed to patients with contraindications. However, there are intermittent reports of fatal lactic acidosis. These fatalities are nearly always associated with the use of intravascular iodinated contrast media for radiological investigations. Such patients commonly have underlying renal disease and develop acute renal failure in association with the use of contrast media and then develop marked metformin accumulation.[15]

Stopping metformin temporarily for the investigation should diminish the risk of lactic acidosis. However, there is much disagreement as to the appropriate schedule to follow.[16] The Royal Australian and New Zealand College of Radiologists recommends no withdrawal of metformin in patients with normal renal function and contrast doses up to 100 mL. Patients with impaired renal function should suspend metformin for 48 hours from the day of the procedure and recommence when a test of renal function shows no deterioration.[17] In patients undergoing urgent investigations, adequate intravenous hydration should be maintained to preserve renal function. Prolonged withdrawal of metformin may lead to hyperglycaemia and consequent dehydration. This may cause acute deterioration in renal function in patients with diabetes and pre-existing renal disease.

Pre-diabetes

In a randomised trial, metformin reduced the risk of developing type 2 diabetes by around 30% in high-risk patients. However in the same study, interventions with diet and exercise were twice as effective as metformin in preventing diabetes.[18]

Conclusion

Metformin is the drug of first choice in the management of hyperglycaemia in type 2 diabetes. It improves mortality in obese patients with diabetes. The risk of gastrointestinal adverse effects is common. In patients with diabetes, the risk of lactic acidosis in metformin users does not appear to be higher than in non-users. However, the use of intravascular iodinated contrast material in association with metformin may pose the greatest risk of lactic acidosis.

Metformin can be continued despite some of the contraindications in the product information if the dose is reduced in appropriate patients and stopped at the time of acute illness. Warnings about the use of metformin in pregnancy and breastfeeding should be reviewed. <

Conflict of interest: none declared

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SELF-TEST QUESTIONS

True or false?

1. Metformin is always contraindicated in lactation.
2. Vitamin B_{12} should be measured periodically in patients taking metformin.

Answers on page 35

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Letters to the Editor

Rational use of topical corticosteroids

Editor, – In the article on topical corticosteroids (Aust Prescr 2013;36:158-61) there is no reference to the oral mucosa. Some steroid preparations have long been used as effective treatment for conditions in the mouth, notably for lichen planus.[1] One option is 0.05% betamethasone ointment. This has proved particularly relevant in over 20 years of practice, as I am contacted periodically by pharmacists questioning if such a prescription is appropriate for use on the oral mucosa.

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Pablo Fernández-Peñas, one of the authors of the article, comments:

Some mucosas have stratified epithelium similar to the skin, but with thinner or non-existent stratum corneum. This changes the absorption of molecules. In a cream or ointment there are more components than the corticosteroid, and I do not have enough information to assess that it is safe to use skin products in the oral mucosa.

The clinical outcome will depend on making a correct diagnosis and applying the right molecule in the most appropriate vehicle for the correct duration. In this regard, there may be vehicles that are not adequate for the oral mucosa. Most dermatologists tend to compound their topical corticosteroids in 'orabase' for use on mucosas, to be on the safe side.

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