Re/fining metformin prescribing in New Zealand

Sisira Jayathissa, Paul Dixon, Raymond Bruce, David Reith

ABSTRACT
Metformin is the mainstay of treatment of type 2 diabetes. However, there has been significant concern on prescribing metformin in patients with renal impairment as a result of metformin-associated lactic acidosis (MALA). Recent studies have cast doubt on the existence of MALA purely related to metformin use. Medsafe recently initiated changes to datasheet so lower doses of metformin could be used in patients with GFR down to 15ml/min. In this paper we outline the context and implications of this change.

For many years metformin has been the mainstay of pharmacological treatment of patients with type 2 diabetes. The International Diabetes Federation,1 the American Diabetes Association2 and European Association for the Study of Diabetes3 recommend that metformin be commenced as the first-line treatment in all newly diagnosed patients, regardless of age.

The discovery of metformin can be traced back to the pioneering work with extracts of the herb Galega officinalis in early 20th century, which led to the characterisation of the blood-lowering effects of an active ingredient named galegine.4 Metformin has a significant effect on blood glucose levels and reduces mortality compared to other therapeutic modalities and the risk of cardiovascular disease.5,6 Based on medium-sized cohort study with 10-year follow-up, metformin may be associated with a reduction in cancer risk.6,7 It helps in weight reduction and seems to prolong survival in experimental models,8 and will be tested for anti-aging effect in humans.9

In general, metformin is well tolerated, although may cause nausea, vomiting or diarrhoea in some patients, especially if introduced at a high dose or taken on an empty stomach. Vitamin B12 deficiency is a less common side effect, and occasional measurement of Vitamin B12 levels in patients on long-term metformin therapy is prudent.10 Lactic acidosis is a spectre that has hung over metformin ever since its introduction because other biguanides, phenformin and buformin (long since withdrawn from the market) were clearly associated with an increased rate of lactic acidosis. This association has resulted in application of restrictions on use of metformin, not taking into account the different pharmacokinetics. The question arises as to whether metformin can induce lactic acidosis on its own, and in the normal course of events the answer is probably no, or if it does, it is exceedingly rare. However, metformin is known to raise lactate levels in humans but magnitude of this increase is small. Overdose of metformin can result in raised lactic acid levels and in serious overdose, lactic acidosis may occur even in healthy individuals.11 In animals and humans, metformin administration is associated with an increase in blood lactate levels. The increase in plasma lactate concentration with therapeutic doses of metformin is small, usually <2mmol/L, although higher levels may occur.12 In patients with lactic acidosis, lactate levels are usually raised above 5mmol/L. Lactic acidosis is most commonly associated with tissue ischaemia such as in septic shock, burns, limb ischaemia, seizures, trauma, severe dehydration, cardiac arrest or cardiogenic shock, and may be aggravated by hepatic and renal dysfunction, alcohol, respiratory insufficiency and elevated levels of metformin. It is likely that in most cases of lactic acidosis occurring in patients taking metformin, other causes have been major contributors. Metformin-associated lactic acidosis (MALA) has a high mortality, but the rates have decreased from 50% to 25% in recent studies.13
A Cochrane review failed to identify any cases of lactic acidosis in patients taking metformin. However, a Dutch observational study found an incidence of 47 cases of metformin-associated lactic acidosis per 100,000 patient years, but the outcome of MALA was determined by the severity of the underlying disease rather than by metformin itself. However, in other studies the highest estimates are ≤10 events per 100,000 patient-years of exposure. Even though large-case series have given polar opposite results, cases of lactic acidosis associated with metformin use have been reported regularly. There may be a link between metformin use and lactic acidosis, though a systematic review suggested that other factors may be implicated.

Renal impairment is a particular risk in patients with type 2 diabetes, in part because of the incidence of diabetic nephropathy, but they are also usually in an older age group and they may have co-morbidities, such as hypertension, that may play an aetiological role in renal damage. Metformin is not metabolised in the body, but transported through the body by transporters and is actively excreted unchanged by the kidneys. Reduction in glomerular filtration rate reduces active excretion of metformin and can be associated with an increase in plasma concentration of the drug. It is considered that a plasma metformin level of <5mg/L is safe and does not carry any significant risk of lactic acidosis. Previous advice has been that metformin was contraindicated in patients with a creatinine clearance <60mL/min. However, some health authorities have reset the contraindication at 30ml/min.

Recently an Australian group has studied pharmacokinetics of metformin, both normal and sustained release preparations in healthy subjects and patients. The group assessed dose-response curves of metformin in healthy subjects and patients with type 2 diabetes, and then by modelling have developed maximum metformin doses in relation to creatinine clearance that will maintain plasma metformin levels <5mg/L. Medsafe has evaluated this data and have now made changes to the New Zealand data sheet for metformin, incorporating the information from this paper. These recommendations are shown in Table 1.

In practice GFR is often estimated using alternative methods to Cockroft Gault, such as the MDRD or CKD-EPI equations, and also adjusted to a surface area of 1.73m². All these equations produce an acceptable estimation of GFR, although in patients with lower GFR, the MDRD and CKD-EPI equations have higher accuracy compared to the Cockroft-Gault. The CKD-EPI equation was developed using measured GFR that was adjusted for surface area (ref Levey et al 2009). When using GFR expressed as mL/min/1.73m² to adjust dose, patients who have a low surface area may as a result be overdosed, and patients with a high surface area may be underdosed. Hence, at extremes of body size it would be advisable to base the dose adjustment on total GFR, expressed in mL/min, instead of GFR adjusted for surface area, expressed as mL/min/1.73m². The conversion can be performed by multiplying the estimate of GFR expressed as mL/min/1.73m² by the patients surface area divided by 1.73m².

Metformin dose reduction has been recommended by Medsafe below eGFR 60mL/minute. However, NICE guidelines suggest review of dose of metformin if eGFR is below 45mL/min, and stopping metformin at GFR below 30ml/minute. Australian guidelines suggest reduction of metformin dose to 1,500mg daily between eGFR 45–60mL/minute and maximum of 850mg daily if eGFR is between 30–45ml/minute. According to Lipska, there is clear recognition that renal failure may be a risk factor for adverse events with metformin use, but

<table>
<thead>
<tr>
<th>Creatinine clearance</th>
<th>Maximum daily dose of metformin</th>
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<tbody>
<tr>
<td>15–30mL/min</td>
<td>500mg</td>
</tr>
<tr>
<td>30–60mL/min</td>
<td>1000mg</td>
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<tr>
<td>60–120mL/min</td>
<td>2000mg</td>
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Table 1: Recommendation of metformin dose based on creatinine clearance (Doung et al).
there is significant divergence in opinion across the globe regarding the optimal definition of safety. All guidelines concur about the need for review and reduce some of the higher doses (2.5–3.0g daily) encountered in clinical practice when GFR is lower.

The main message to practitioners is to consider progressive dose reduction and monitoring in renal impairment, while maintaining the pharmacological benefits of therapy down to a GFR as low as 15mL/min based on current Medsafe recommendations. Therefore patients may not need to change to other medication early, which could be less desirable and also not available under New Zealand pharmaceutical benefits scheme. It is likely that higher dosage of metformin has been continued in many patients with moderate renal failure without appropriate guidance or dose adjustment, which perhaps contributed to some cases of lactic acidosis, so using lower doses may lead to safer use of metformin.

However, there are some unresolved issues. These recommendations are not based on randomised controlled trial data or chronic treatment pharmacokinetics, and this need to be addressed by long-term studies. It is equally important to conduct further research into therapeutic efficacy of metformin in patients with normal renal functions to identify maximum effective and safe dose and its relationship to metformin levels. Efficacy of metformin at lower doses in patients with renal failure has also been questioned by some and needs to be studied further. In addition, according to Medsafe guidance, highest recommended daily dose in patients with normal renal functions is two grams, less than the commonly used daily dose of up to three grams, and it is not clear that dose reduction may lead to loss of therapeutic efficacy and practitioners need to be vigilant about this potential. It is well known that lower doses of metformin work in early type 2 diabetes, and so it is likely to be effective in patients with renal impairment. There may be a case for metformin measurements when used in patients with very low GFR, but the assay is not routinely available in New Zealand. Measurement of venous lactate levels may be a potential alternative in high-risk situations.

Metformin should not be used when the GFR is <15mL/min. Adam et al predicted plasma metformin level of 4.4mg/litre at GFR of 10mL/min when 500mg/day metformin dose was used. Although the risk of MALA does not seem to be increased, and the progression to end-stage renal disease is significantly lower, patients on metformin at this level of renal function have significantly higher all-cause mortality.

Like many other medicines, prescribers need to be vigilant for side effects and adjust the dose of metformin accordingly, but unfortunately this is often forgotten. Renal function should be checked regularly in patients on metformin. We suggest renal function testing annually for patients with creatinine clearance >80mL/min, six monthly for patients 30–80mL/min and three monthly for patients <30mL/min or more frequently in patients at particular risk of renal function deterioration, eg commencement of ACE inhibitors or NSAIDs. Metformin doses should be adjusted according to the eGFR.

Medsafe is to be congratulated for their initiation of these changes for metformin in the context of renal impairment. This is unusual, where the regulatory agency takes an active step in improving dosing recommendations. Suggested changes should allow continuation of this valuable medication at a lower dose in patients with type 2 diabetes, despite declining renal function. Several authors have advocated the liberalisation of metformin therapy in the context of renal impairment. Patients should be warned to discontinue metformin during serious acute illness especially leading to dehydration and serious infections to minimise any aggravation of the risks for lactic acidosis. Insulin can always be used as a short-term substitute for glycaemic control. Question of maximum effective dose in patients with normal renal functions need to be clarified with further research. Prescribers should be vigilant in monitoring side effects and reporting them to CARM (Centre for Adverse Reaction Monitoring), especially when used in patients with moderate to severe renal impairment. These reports can be made electronically through the CARM website.
Competing interests:
Dr Jayathissa is a member of Medicine Adverse Reaction Committee (MARC), a ministerial advisory committee for Medsafe. MARC committee endorsed Medsafe changes to metformin data sheet. Associate Professor David Reith is chair of the MARC committee.

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