

EDITORIAL

A safe and effective drug?

Matthew P Doogue

A safe drug is an oxymoron. Any substance with pharmacological effects can cause harm and if a substance is harmless it has no effect. The potential harms of a medicine is one of two factors that limits medicine use, the other being cost. Knowing the potential harms (adverse effects) of a medicine and mitigating the risk of harm in individual patients is at the core of therapeutics.

In New Zealand there are about 1700 registered medicines, each medicine capable of causing several effects. The probability of each of those effects occurring is dependent on patient factors and drug exposure. Identifying circumstances of increased risk is codified in “contraindications” and “precautions”. Of particular difficulty for prescribers is that those who are most likely to benefit from a drug are often also those at greatest risk of harm.

Of these 1700 medicines only a handful can be generally described as effective, safe and cheap, and one of these is metformin. Metformin is effective and stands alone as first-line pharmacotherapy for type 2 diabetes. Metformin is cheap with the New Zealand community pharmaceutical schedule price \$1.23 for 100 500 mg tablets, about \$20 a year per patient.¹

Metformin is mostly safe with the most common harm of metformin being nausea and diarrhoea affecting up to one-third of patients. This can be monitored by symptoms and managed by dose titration in most patients. Discontinuation is required in 1–5% of patients.² The most feared harm of metformin, lactic acidosis, is very rare and can be avoided by avoiding metformin use in those at highest risk.³ The third notable harm of metformin, less well known to prescribers is vitamin B12 deficiency.

In this issue of the *Journal*, Haeusler and colleagues report a 17% prevalence of B12 deficiency in a cross-sectional study of New Zealand patients.⁴ While one could quibble about methodology (e.g. the lack of a comparator group) the primary finding is strong and important to clinical practice. It is strong because no matter the confounders this result is likely to be statistically and clinically significant. It is important because we can do something about it, vitamin B12 deficiency is easily diagnosed, easily treated and treatment improves outcomes.

That metformin causes malabsorption of vitamin B12 was demonstrated more than 40 years ago.⁵ Authors at the time advocated annual laboratory measurement of vitamin B12 and this has been included in the product information continuously since the 1970s. Subsequent clinical studies have demonstrated megaloblastic anaemia associated with metformin can be easily diagnosed and treated with vitamin B12 without stopping metformin.⁶

Despite this, current international and regional guidelines for treating diabetes seldom comment on the risk of B12 deficiency and metformin, although they often mention checking for vitamin B12 deficiency in the differential diagnosis of peripheral neuropathy.⁷⁻⁹ Most drug formularies, including the New Zealand Formulary, mention B12 deficiency as an adverse effect but provide no guidance for clinicians about risk mitigation, including testing.

What are the implications for prescribers in New Zealand? Firstly metformin-induced B12 deficiency is an adverse drug reaction with a high prevalence, 17% in this study and similar in many other studies. Secondly B12 deficiency is asymptomatic early on and when symptomatic one of the manifestations, peripheral neuropathy, is also a complication of the disease being treated. Hence, unlike gastrointestinal (GI) intolerance, it won't be detected by symptoms alone. Thirdly the neurological effects of vitamin B12 deficiency are permanent. Fourthly vitamin B12 deficiency can be detected readily by cheap widely available blood tests. Fifthly vitamin B12 is safe, cheap, effective and familiar to most GPs. All in all Haeusler and colleagues make a compelling case for screening.

However annual measurement of serum vitamin B12 concentration, as recommended in the data sheet, may not be justified as the onset of B12 deficiency is gradual and less frequent testing is likely to be effective. Further the threshold to define vitamin B12 deficiency is not universally agreed and measurement of vitamin B12 in serum is not the only test option, with serum homocysteine and/or methylmalonic acid being sensitive biomarkers of B12 deficiency. Measurement of a baseline serum vitamin B12 concentration and a full blood count around the time of initiation of metformin is pragmatic. In most cases other blood tests will also be indicated and the incremental cost of these tests is modest. How often to perform subsequent tests, in the absence of symptoms is not clear and further guidance is needed. In the absence of guidelines, rechecking serum vitamin B12 every 2–5 years in a patient treated with metformin seems reasonable.

The real cost of drug treatment is never just the price of the drug. Monitoring the effects (beneficial and harmful) and managing harms is necessary for all drug treatments. Several new drugs have come to market, notably the new oral anticoagulants, claiming minimal monitoring is required and claiming consequent savings for the health system.

The reality is that even the safest drugs require careful monitoring to mitigate patient harm. While harms from medications can never be completely avoided, we have a duty to reduce them where we can.

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Author information: Matthew P Doogue, Clinical Pharmacologist and Endocrinologist^{1,2}

1. Department of Medicine, University of Otago, Christchurch

2. Department of Clinical Pharmacology, Canterbury District Health Board, Christchurch

Correspondence: Dr Matt Doogue, Department of Medicine, University of Otago, PO Box 4345, Christchurch, New Zealand. matt.doogue@otago.ac.nz

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