

# Metformin: a multitasking medication

Most current guidelines and algorithms for the treatment of hyperglycaemia in type 2 diabetes suggest metformin as first-choice oral antidiabetic therapy. They point to its antihyperglycaemic efficacy with low risk of frank hypoglycaemia, lack of weight gain, and ability to counter insulin resistance without raising insulin levels. Independent of glycaemic control there are several potentially beneficial effects on cardiovascular risk factors, and evidence of improved cardiovascular outcomes. Additionally, metformin is conveniently combined with any other antidiabetic drug, and there are no significant interactions with the battery of lipid-lowering, antihypertensive and anticoagulant therapies commonly required by type 2 diabetic patients. Monitoring commitments are not arduous, and cost is comparatively low.

Of course there are tolerability issues, and important contra-indications that must be respected for metformin, but with 50 years of clinical use to reflect upon, the verdict is overwhelmingly positive. Yet 30 years ago biguanides stood in the dock, their safety criticised and their future bleak. High rates of lactic acidosis sealed the withdrawal of phenformin in most countries at the end of the 1970s, soon followed by the disappearance of another biguanide, buformin. Accusing fingers pointed at respiratory chain disruption and impaired oxidative metabolism with phenformin. Ironically, shortly after phenformin was withdrawn, evidence emerged that a genetic variation in the ability to metabolise phenformin affects about 9% of the population, explaining an accumulation of the drug in such individuals and their susceptibility to lactic acidosis. But the era of pharmacogenomics had still to dawn.

Metformin survived, just. It is not metabolised (or hardly so) in man, but it can accumulate if renal impairment goes unrecognised. Raised concentrations of metformin may interfere with oxidative metabolism, but much less so than with phenformin, and it is well appreciated that the detrimental effects of excess lactate are considerably greater in hypoxaemic states. However, metformin-associated lactic acidosis is rare (with an incidence of less than 0.1 and probably about 0.03 cases per 1,000 patient-years of treatment), and confidence in this agent has reached an all-time high. The benefit:risk balance of metformin has encouraged some commentators to question whether the constraints on its usage might be relaxed. But one reason for the continued popularity of the drug may be its judicious use, and continued insistence that all precautions continue to be heeded.

Metformin exerts a variety of cellular actions in different tissues at different drug concentrations and in different metabolic states. These actions are individually modest but collectively sufficient to confer the efficacy and breadth of therapeutic effects against diabetes and its vascular complications. The diversity of cellular actions may yet extend the medicinal value of metformin, as evidence emerges for helpful effects in the treatment of other insulin-resistant states such as polycystic ovarian syndrome (PCOS), nonalcoholic fatty liver disease (NAFLD) and the metabolic disturbances that accompany human immunodeficiency virus (HIV). Most recently, preliminary reports have raised the possibility that metformin could have some anti-tumour effects. The field of therapeutics is strewn with descriptors such as panacea, pleiotropic and holistic, so why not multitasking for metformin?