

## Metformin and serious adverse effects

### *Attention to known contraindications and intercurrent illness can avoid life-threatening acidosis*

**METFORMIN**, A BIGUANIDE DERIVATIVE, has been used in the treatment of type 2 diabetes for nearly 50 years. It acts as an insulin-sensitising agent, lowering fasting plasma insulin concentrations by inducing greater peripheral uptake of glucose, as well as decreasing hepatic glucose output.

In 1998, the United Kingdom Prospective Diabetes Study reported that, in overweight patients with type 2 diabetes, treatment with metformin compared with diet alone resulted in statistically significant absolute risk reductions (ARRs) in all-cause mortality (ARR, 7%), diabetes-related deaths (ARR, 5%), any diabetes-related endpoint (ARR, 10%), and macrovascular disease (myocardial infarction, sudden death, angina, stroke, peripheral vascular disease).<sup>1</sup> This was achieved without hypoglycaemia or weight gain. As a result, metformin is now regarded as the oral hypoglycaemic agent of choice in the treatment of overweight people with type 2 diabetes.

More recently, the use of metformin has broadened, with evidence for its benefit in other insulin-resistant states. In polycystic ovary syndrome, metformin decreases insulin resistance, restores ovulatory menses, facilitates conception, and reduces the rate of first-trimester spontaneous abortion.<sup>2</sup> Metformin also delays progression to type 2 diabetes in people with impaired glucose tolerance.<sup>3</sup> It is currently being evaluated in the treatment of gestational diabetes mellitus, and has shown promising results in selected individuals with type 1 diabetes.<sup>4</sup>

But this increase in the use of metformin is not without risk. The manufacturer's product information on metformin reminds prescribers that life-threatening lactic acidosis can occur, caused by accumulation of metformin, and that risk factors for this include renal impairment, old age and doses over 2 g per day. The estimated prevalence of life-threatening lactic acidosis is one to five cases per 100 000,<sup>5</sup> with mortality in reported cases up to 50%.<sup>6</sup> Traditionally, this complication has been thought of as secondary to an accumulation of the drug. Metformin is excreted unchanged in the urine, with the half-life prolonged and renal clearance decreased in proportion to any decrease in creatinine clearance.<sup>6</sup> This may occur chronically in chronic renal impairment, or acutely with dehydration, shock, and intravascular administration of iodinated contrast agents, all of which have the potential to alter renal function. Tissue hypoxia also has a significant role, and acute or chronic conditions

that may predispose to this condition, such as sepsis, acute myocardial infarction, pulmonary embolism, cardiac failure and chronic liver disease, may act as triggers.

Between 1985 and 2001, 48 cases of lactic acidosis with metformin were reported to the Australian Adverse Drug Reactions Advisory Committee (ADRAC). In 15 of these cases, the complication was fatal. In 35 of the 48 cases, known risk factors were identified. Over the past 4 years, the average number of cases reported to ADRAC has been six per annum. In Australia in 2002–2003, about 200 000 patients were prescribed metformin, giving a reported frequency of lactic acidosis of one in 30 000. However the actual rate of occurrence is likely to be higher, given that under-reporting is an inherent problem with voluntary pharmacovigilance programs.

At the Princess Alexandra Hospital in Brisbane, since January 2000, we have identified 13 patients with lactic acidosis thought to be related to use of metformin. Of these 13 patients, two died, while three require ongoing dialysis for renal failure; another was left with severe neurological disability requiring nursing-home care. The average age of the affected patients was 67 years (range, 47–79 years), and the baseline serum creatinine concentration (known in 10 patients) ranged from 0.12 mmol/L to 0.48 mmol/L, with a mean of 0.21 mmol/L (reference range, 0.05–0.11 mmol/L in women, and 0.06–0.12 mmol/L in men). Seven of the 13 patients were taking a metformin dose of 3 g per day, three were taking 2 g, while the remaining patients were taking between 500 mg and 1.7 g.

How well do we currently comply with recommendations on prescribing metformin? A study at the University of Pittsburgh Medical Center in the United States reported on 263 hospital admissions involving 204 patients who were taking metformin. Patients had at least one absolute contraindication to metformin in 27% (71) of admissions. In 41% (29) of these, treatment with metformin continued despite the contraindication.<sup>7</sup> A Scottish study of 1847 patients taking metformin found that 24.5% (452) had a contraindication.<sup>8</sup>

It follows that metformin must be prescribed appropriately to avoid potential adverse effects, while offering patients the best treatment possible.

In well, ambulatory patients, renal function should be monitored regularly. A cut-off serum creatinine concentra-

tion above which metformin should be discontinued has been arbitrarily set at 0.15 mmol/L.<sup>9</sup> Obviously, this needs to be individualised, and age, muscle mass, and protein turnover need to be considered. This can be achieved using the Cockcroft–Gault equation, which estimates creatinine clearance from age, weight and serum creatinine concentration. For example, with this equation, a 75-year-old woman, weighing 65 kg, with a serum creatinine concentration of 0.11 mmol/L, has an estimated creatinine clearance of 40 mL/min, which is significantly reduced. We propose:

- setting an absolute cut-off point (a creatinine clearance of 30 mL/min), below which metformin should be discontinued; and
- using metformin with extreme caution in patients with a creatinine clearance in the range 30–50 mL/min.

No clear guidelines exist on reducing the dose of metformin as renal function declines, but reports of lactic acidosis have occurred with doses as low as 500 mg per day. Alternative strategies for managing diabetes in this situation include the use of insulin, thiazolidinediones and sulfonylureas.

The second adverse situation to be considered is the previously well patient with a significant intercurrent illness. This includes illnesses with the potential to alter renal function, such as dehydration, shock, and sepsis. Metformin should be ceased completely while the patient is unwell, and recommenced when the illness has resolved, and renal function is shown to be normal. In addition, illnesses that increase the risk of tissue hypoxia and acidosis, such as acute

myocardial infarction, pulmonary embolism, and cardiac failure, can trigger lactic acidosis, and the dose of metformin should be significantly reduced (or the drug discontinued altogether) under these circumstances. Patients need to be educated about these risks. Finally, a special situation is the use of iodinated contrast agents. The current recommendation is that metformin be withheld for 24–48 hours before the procedure and be recommenced 48 hours afterwards and only when renal function is shown to be normal.<sup>10</sup>

Without doubt, metformin remains the drug of choice for most patients with type 2 diabetes. Careful and thoughtful use of this drug has the potential to avoid life-threatening adverse events.

**Janelle C Nisbet**

Endocrinology Registrar

**Joanna M Sturtevant**

Renal Specialist Pharmacist

**Johannes B Prins**

Director of Diabetes and Endocrinology, Princess Alexandra Hospital and Professor of Endocrinology, University of Queensland, Brisbane, QLD  
jprins@soms.uq.edu.au

1. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; 352: 854-865.
2. Glueck CJ, Wang P, Goldenberg N, Sieve-Smith L. Pregnancy outcomes among women with polycystic ovary syndrome treated with metformin. *Hum Reprod* 2002; 17: 2858-2864.
3. Slama G. The potential of metformin for diabetes prevention. *Diabetes Metab* 2003; 29: 104-111.
4. Hamilton J, Cummings E, Zdravkovic V, et al. Metformin as an adjunct therapy in adolescents with type 1 diabetes and insulin resistance: a randomized controlled trial. *Diabetes Care* 2003; 26: 138-143.
5. Brown JB, Pedula MS, Barzilay J, et al. Lactic acidosis rates in type 2 diabetes. *Diabetes Care* 1998; 21: 1659-1663.
6. Bailey CJ, Turner RC. Metformin. *N Engl J Med* 1996; 334: 574-579.
7. Calabrese AT, Coley KC, DaPos SV, et al. Evaluation of prescribing practices: risk of lactic acidosis with metformin therapy. *Arch Intern Med* 2002; 162: 434-437.
8. Emslie-Smith AM, Boyle DIR, Evans JMM, et al. Contraindications to metformin therapy in patients with type 2 diabetes — a population based study of adherence to prescribing guidelines. *Diabet Med* 2001; 18: 483-488.
9. Jones GC, Macklin JP, Alexander WD. Contraindications to the use of metformin. *BMJ* 2003; 326: 4-5.
10. Thomsen HS, Morcos SK. Contrast media and metformin: guidelines to diminish the risk of lactic acidosis in non-insulin-dependent diabetics after administration of contrast media. ESUR Contrast Media Safety Committee. *Eur Radiol* 1999; 9: 738-740. □