

## Metformin therapy in patients with chronic kidney disease

Metformin therapy is limited in patients with chronic kidney disease (CKD) due to the potential risk of lactic acidosis. This open-label observational study investigated metformin and lactate concentrations in patients with CKD ( $n = 22$ ; creatinine clearances 15–40 ml/min) and in two dialysed patients. Patients were prescribed a range of metformin doses (250–2000 mg daily) and metformin concentrations were compared with data from healthy subjects (scaled to 1500 mg twice daily). A subset of patients ( $n = 7$ ) was controlled on low doses of metformin (250 or 500 mg daily). No correlation between metformin and lactate concentrations was observed. Three patients had high lactate concentrations ( $>2.7$  mmol/l) and two had high metformin concentrations (3–5 mg/l), but none had any symptoms of lactic acidosis. Reducing metformin dosage and monitoring metformin concentrations will allow the safe use of metformin in CKD, provided that renal function is stable.

**Keywords:** diabetic nephropathy, metformin, pharmacokinetics, pharmacology, type 2 diabetes

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### Introduction

Metformin is usually the initial treatment for type 2 diabetes. Metformin is largely excreted renally [1], and plasma concentrations can, therefore, increase in patients with reduced renal function.

Although lactic acidosis is rarely associated with metformin therapy, it has a high mortality. It is defined as an arterial pH  $<7.35$  and lactate concentration  $>5$  mmol/l and it has been suggested that patients with lactate concentrations  $>2.7$  mmol/l be monitored carefully [2].

The Product Information states that metformin should not be used when creatinine clearance is  $<60$  ml/min, while other influential sources advise against using metformin when estimated glomerular filtration rate (eGFR) is  $<30$  ml/min/1.73 m<sup>2</sup> (United Kingdom National Institute for Health and Clinical Excellence guidelines [3]) or creatinine clearance  $\leq 30$  ml/min, Australian Medicines Handbook [4]. The Food and Drug Administration guidelines are based on serum creatinine concentrations only [male,  $\geq 1.5$  mg/dl (134  $\mu$ mol/l); female,  $\geq 1.4$  mg/dl (124  $\mu$ mol/l)] [3]. Clinical practise is at variance with these guidelines according to a recent survey where metformin was often prescribed to patients with eGFR as low as 30 ml/min/1.73 m<sup>2</sup> [2]; unfortunately, data on plasma lactate were not available.

This study investigated the plasma concentrations of metformin and lactate in patients with chronic kidney disease (CKD; creatinine clearance  $<40$  ml/min). Our hypothesis is that metformin is tolerated well by patients with low but stable renal function.

### Methods

Twenty-four patients with type 2 diabetes and CKD were enrolled into this open-label observational study. The dosage of metformin, the dose form (immediate-release; extended-release) and other drugs prescribed for diabetes were not altered. Patients provided written, informed consent. The study was approved by the St Vincent's Hospital and University of New South Wales Institutional Ethics Committees (Protocol Numbers: 08209/SVH08/035 and 09280/SVH09/080).

Blood samples ( $n = 1-6$ ) were collected from each patient to assess metformin concentrations. Serial blood samples ( $n = 10$ ) were collected from two patients on metformin immediate-release (12 h dosage interval). Glycated haemoglobin (HbA1c) and plasma concentrations of lactate and creatinine were determined.

A subset of patients with CKD ( $n = 5$ ) or receiving dialysis ( $n = 2$ ; one haemodialysis, one peritoneal dialysis) was prescribed low daily doses of metformin immediate-release, 500 and 250 mg, respectively. Patients were monitored regularly for 6 weeks (eight clinic visits). Multiple in-line pre- and post-filter blood samples were collected from the patient on haemodialysis to determine extracorporeal metformin clearance. Additional assessments of glycaemia (fructosamine, patient-monitored blood glucose) were conducted and patients were asked if any gastrointestinal symptoms were experienced.

Plasma concentrations of metformin in healthy subjects from the literature [5] were compared with enrolled patients. Since the healthy subjects had normal renal function and the dose was 2000 mg daily, concentrations were scaled to the maximum recommended dose of metformin (3000 mg daily). Concentrations of metformin in plasma were determined using a validated, reverse phase high-performance liquid chromatography assay [6].

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**Table 1.** Characteristics of patients (n = 24).

Parameter	Median (range)
Age (years)	73 (51–86)
Weight (kg)	87 (60–126)
BMI (kg/m <sup>2</sup> )	29 (23–41)
Diabetes duration (years)	12.5 (0.2–21)
Metformin dose (mg/day)	1000 (250–2000)
HbA1c (%)	7.6 (5.7–12.4)
Lactic acid (mmol/l)	1.7 (0.8–5.5)
Creatinine clearance (ml/min)*	32 (15–39)

BMI, body mass index; HbA1c, haemoglobin A1c.

\*Excluding the two dialysis patients.

All statistical analyses were performed using GRAPHPAD PRISM 5.0 (GraphPad Software Inc, San Diego, CA, USA). Quantitative variables are presented as median (range) and the Mann–Whitney *U*-test was used to compare clinical characteristics.

## Results

### Patient characteristics

Patients (Table 1) were generally well-controlled [median HbA1c, 7.6% (60 mmol/mol)] but three patients had poor glycaemic control [HbA1c >10% (86 mmol/mol)]. The median metformin dose was 1000 mg daily (range: 250–2000 mg), with four patients taking metformin extended-release. Patients taking the highest metformin dose (n = 4; 2000 mg daily) did not have better glycaemic control (p = 0.31) than the other patients.

### Metformin concentrations

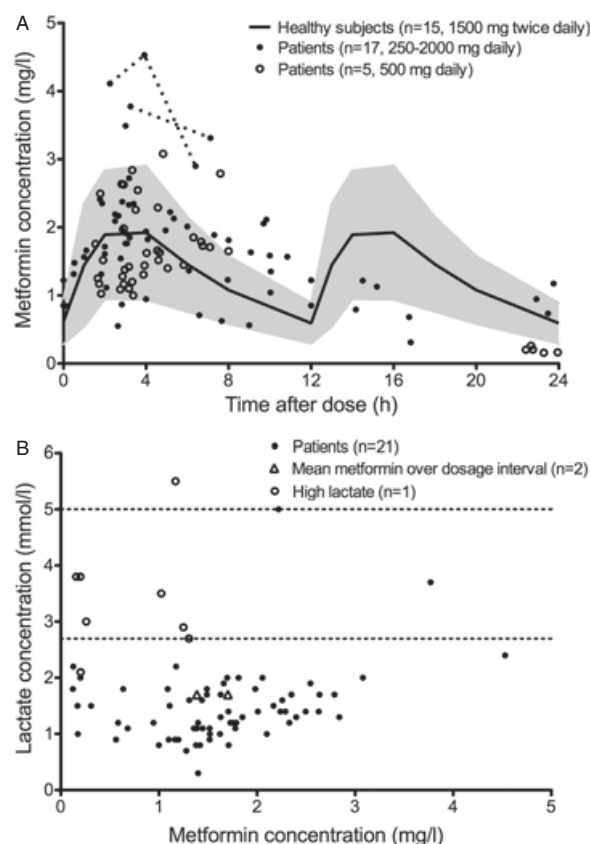
A total of 135 metformin concentrations were determined for 24 patients with CKD. Concentrations were compared with those from healthy subjects (figure 1A). Extracorporeal metformin clearance during haemodialysis was 149 ml/min, at a plasma flow rate of 195 ml/min. About 14% of the daily dose was extracted during a single dialysis session (5 h). Although the clearance of metformin was not determined in the patient on peritoneal dialysis, random metformin concentrations did not exceed 2 mg/l.

### Safety

No patients in the subset group experienced gastrointestinal or other adverse effects. There were no significant changes in the glycaemic control, as assessed by HbA1c, fructosamine and fasting blood sugar concentrations.

Plasma concentrations of lactate did not significantly correlate with either metformin concentrations (figure 1B) or metformin dose (data not shown). Two patients had higher metformin concentrations (3–5 mg/l) but the lactate concentrations were normal.

Three patients had higher lactate concentrations (>2.7 mmol/l) including an obese patient (128 kg) whose lactate concentrations were consistently >2.7 mmol/l (seven of eight



**Figure 1.** Metformin concentrations in patients and healthy subjects and the correlation between metformin and lactate concentrations. (A) Metformin concentrations in healthy subjects (n = 15, Timmins et al. [5]) were scaled to 1500 mg twice daily, the data are shown as mean and 95% confidence interval (shaded area). Excluding dialysis patients, metformin concentrations were compared with patients on range of doses (n = 17), and a subset of patients on low metformin doses (n = 5). Patients with high metformin concentrations are shown with connecting dotted lines (n = 2). (B) The correlation between metformin and lactate concentrations in patients with either paired blood samples (n = 21) or calculated average metformin concentrations over a dosage interval. One patient had consistently high lactate concentrations. Cut-off lines are drawn at lactate concentrations of 2.7 mmol/l (elevated concentration) and 5 mmol/l (hyperlactatemia).

clinic visits over 6 weeks). On one occasion, this patient had a lactate concentration of 5.5 mmol/l, but this may have been due to the patient's immediate prior physical activity. Repeated biochemical measures did not indicate lactic acidosis in any of these three patients; plasma bicarbonate concentrations were within the reference range (24–31 mmol/l at St Vincent's Hospital). Metformin treatment was continued in all three patients.

## Discussion

The most important finding of this study is that metformin was tolerated well by patients with impaired renal function and that there was no correlation between the plasma concentrations of lactate and metformin. One previous study found that metformin was tolerated in patients with eGFR <30 ml/min,



although lactate concentrations were not reported [7]. Notably, while some lactate concentrations in this study were  $>2.7$  mmol/l, metformin was tolerated well and there was no evidence of acidosis. In agreement with the study of Davis et al. [2], dosage with metformin was maintained.

There was large inter-patient variability in the metformin concentrations and they were generally much higher than the therapeutic range ( $0.5 \pm 0.4$  mg/l) suggested by Lalau et al. [8]. However, these authors did not specify the timing of blood collection and their therapeutic range only covers the approximate trough plasma concentrations (figure 1).

Apart from poor compliance, an important consideration, at least two additional factors may have contributed to the variable concentrations of metformin. First, the oral availability of metformin is highly variable, ranging at least threefold (25–75%) [1,9]. Second, there is substantial scatter in the relationship between the renal clearances of metformin and creatinine [9,10]. Therefore, monitoring metformin concentrations may be useful due to the large variability in its pharmacokinetics.

In the patients receiving dialysis, low doses of metformin (250 mg daily), neither metformin concentrations nor lactate concentrations were elevated. This is despite lactate being present in the solutions used in peritoneal dialysis.

Currently, clinicians are faced with the question of whether or not to prescribe metformin to patients whose creatinine clearance is below 60 ml/min. From the present and other studies [7,11], physicians commonly prescribe metformin below this level of renal function despite the guidelines and the product information. Furthermore, it has been argued that metformin is the safest drug to use in patients with renal impairment, provided that renal disease is stable [12].

This study indicates that using metformin at stable creatinine clearances as low as 20 ml/min is safe and provides a basis for undertaking larger, controlled trials of metformin in patients with CKD. However, it is important that the dosage be reduced in renal impairment and only increased after consideration of the blood glucose and plasma concentrations of lactate. Measurement of metformin concentrations is useful to ensure no significant drug accumulation in patients with CKD but patients need to be aware of warning signs for lactic acidosis such as nausea and vomiting.

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## Conflict of Interest

The authors have no competing interests. J. D. researched data, collected and analysed the data and drafted the manuscript. T. F., J. G. and R. D. were responsible for the study idea and design of the subset study. D. R. and T. F. provided medical consultations for subset patients. J. D. and G. G. were involved in the literature review. All authors were involved in the interpretation of results, contributed to the manuscript preparation and granted final approval of this report.

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