Metformin use in chronic kidney disease: new evidence to guide dosing

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Metformin controls blood glucose, does not cause hypoglycaemia or weight gain and has been shown to reduce the long-term complications of diabetes, including macrovascular disease.1 Since metformin is renally cleared, there is a genuine risk of metformin accumulation and associated lactic acidosis in chronic kidney disease (CKD). We have previously argued that there is disproportionate fear surrounding the safety of metformin in CKD, with important side effects from alternative agents ignored. Both the risk of hypoglycaemia with sulphonylureas or insulin and risk of heart failure with thiazoladinediones are expected to increase as CKD progresses, and are at least as large as the risk of lactic acidosis.2 Moreover, the mortality from metformin-induced (i.e. pure type B) lactic acidosis appears substantially smaller than the 50% observed with other more common causes of lactic acidosis.3

Nevertheless, the current UK’s National Institute for Clinical Excellence guidelines advise that metformin should be reviewed if the serum creatinine exceeds 130 µmol/l [or estimated GFR (eGFR) is below 45 ml/min/1.73 m²], and stopped when creatinine rises above 150 µmol/l (or eGFR falls below 30 ml/min/1.73 m²).4 Dosing recommendations from other bodies also advise a renal function threshold after which metformin becomes unsafe, but agreement is rare,5 with most not providing specific dosing advice. However, it is important to recognize that stopping metformin in CKD may deprive patients of its macrovascular benefits at the very time vascular risk begins to substantially increase.

Metformin requires membrane-based transporters to facilitate absorption from the gut, distribution into hepatocytes and clearance by the kidneys. Several genetic variants that affect in vitro transporter activity have been identified, which, together with dietary factors, have been hypothesized to be responsible for the variability in the proportion of each dose of metformin that is absorbed (oral bioavailability ranges from 40 to 70%).6

Intravenous dosing studies inform us that it is difficult to quote an accurate half-life for metformin because its elimination is multiphasic with a long terminal phase and that metformin is almost exclusively eliminated in the urine. Clearance is ~500 ml/min, over four times GFR, indicating that metformin is actively secreted by the renal tubules (in addition to the glomerular filtration expected from a small water-soluble non-protein bound drug).6 There is a linear correlation between creatinine clearance (CrCl) and metformin clearance; those with lower GFR have proportionally lower metformin clearance.6 However, there is variation in metformin concentration that may not be explained by measured renal function alone and polymorphisms in renal proximal tubular expressed transporters OCT1 and 2 and MATE1 and 2K have been hypothesized to influence clearance.6

Population pharmacokinetics uses sparse sampling of many individuals (rather than intensive
sampling a small number of individuals). This approach has the advantage that a wider selection of potential determinants of drug handling (including genetic polymorphisms) can be investigated. A recent population model by Duong et al. considers, for the first time, the relative importance of both transporter genetic variants and renal function on metformin clearance, providing the best evidence to date to guide metformin dosing in CKD.7

Duong et al.’s population model considered age, Cockcroft–Gault (C–G) CrCl and 59 common genetic variants of the OCT and MATE transporters. The model included 4895 metformin plasma concentrations measured in 305 individuals (Caucasians and Malaysians), including 52 with a CrCl <60 ml/min (minimum = 15 ml/min). Key determinants of metformin concentration were identified as total body weight and C–G CrCl, but not transporter polymorphisms. The finding that no common transporter variant significantly influenced metformin pharmacokinetics simplifies metformin dose adjustment. Using their model to simulate the range of metformin concentrations that might be expected with different CrCls, Duong et al. predicted that 95% of patients with CrCls of 15, 30, 60 and 120 ml/min would have peak plasma metformin concentration <5 mg/l (an estimate from several studies of metformin concentration which does not increase lactate6,8,9 without tapering of any hypoglycaemic effect10), if maximum daily doses were restricted to 500, 1000, 2000 and 3000 mg, respectively (Table 17). These substantial dose reductions also minimized drug exposure despite slower clearance.

It is unnecessary to formally measure GFR to guide metformin prescription in CKD, as the gain in precision over C–G CrCl is small relative to variation in metformin bioavailability. Metformin levels (plasma or whole blood), therefore, might be needed to reassure some prescribers that CKD patients are receiving a safe dose at low GFR. Indeed, it would be unwise to continue metformin as patients approach end-stage renal disease without monitoring metformin concentration closely (note that there are reports of a safely monitored dialysis patients taking metformin9). However, as metformin assays are not widely available, most prescribers must rely solely on the available pharmacokinetic evidence (Table 1). If, after counselling for the risks and benefits of all hypoglycaemic agents, a CKD patient chooses to continue dose-reduced metformin, then ‘sick day rules’ should include stopping of metformin if diarrhoea, vomiting, dehydration, worsening shortness of breath or unexplained lethargy develop (all symptoms that may represent metformin-associated lactic acidosis or predispose to it).

<table>
<thead>
<tr>
<th>C–G CrCl (ml/min)</th>
<th>Maximum daily dose of metformin (mg)</th>
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<tbody>
<tr>
<td>120</td>
<td>3000</td>
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<tr>
<td>60</td>
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<td>30</td>
<td>1000</td>
</tr>
<tr>
<td>15</td>
<td>500</td>
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*aBased on ideal body weight.  
bImmediate release preparation.

C–G CrCl (ml/min) = ([140 – age in years] × [mass in kg] × [1.23 for males or 1.04 for females]) ÷ (serum creatinine in μmol/l).

Finally, because it is uncertain whether alternative hypoglycaemic agents are better than metformin in diabetics with an eGFR of <30 ml/min/1.73 m2,2 a randomized trial is indicated. Metformin-associated lactic acidosis is such a rare event (indeed no cases have been observed in 70,490 patient-years of patients taking metformin in trials11), so a trial comparing a policy to continue on metformin in advanced CKD (with monitoring of metformin levels) vs. a switch to an alternative hypoglycaemic agent would have to be extremely large to provide a clear answer on safety. However, if the expected benefits on macrovascular events with metformin are real,1 a trial of a few thousand CKD patients might be sufficiently powered to test whether a policy to continue metformin in CKD is of net benefit. Therefore, until a randomized trial proves either way, offering the opportunity to continue metformin carefully selected, counselled and monitored CKD patients appears reasonable—and now there is good evidence to guide appropriate dose reduction.

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**References**


