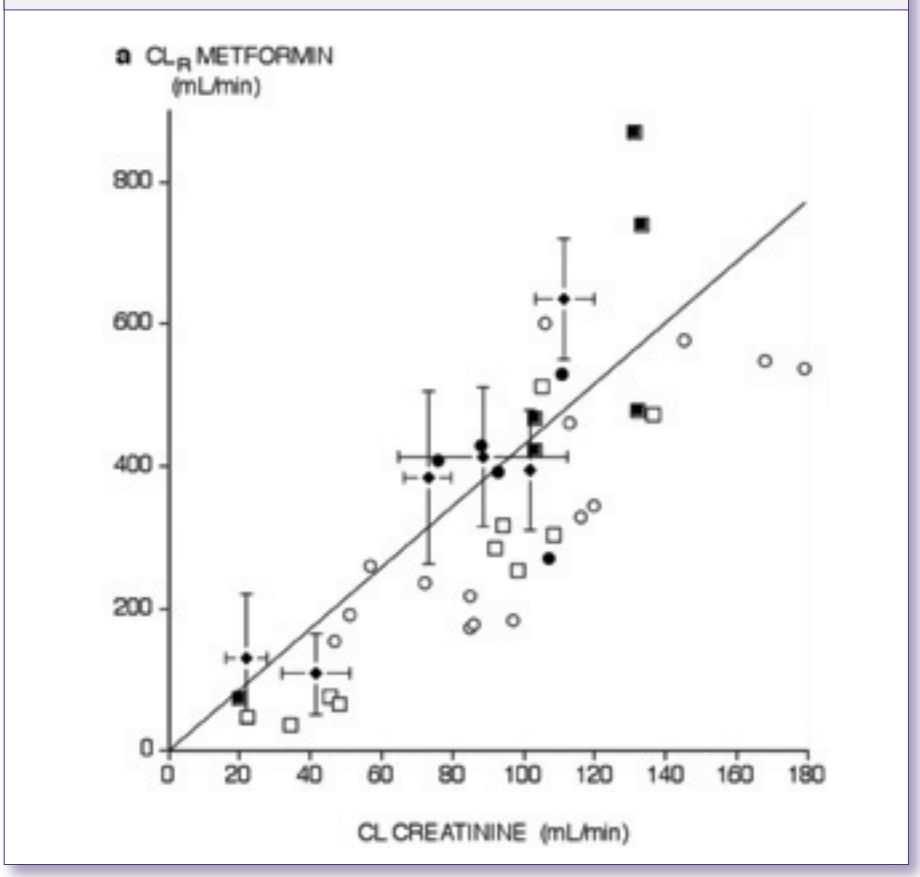
The use of metformin in diabetic patients with renal impairment

Metformin is widely used for the treatment of Type 2 diabetes but there have been questions about its association with lactic acidosis. Metformin is primarily excreted unchanged in urine and its renal clearance is approximately proportional to the clearance of creatinine. Lactic acidosis is uncommon during treatment with metformin but excessive accumulation may exacerbate lactic acidosis. The dosage of metformin should be reduced in line with impairment of renal clearance as calculated by creatinine clearance or eGFR. We consider that metformin can be used in patients with creatinine clearances down to 30 mL/min provided that renal function is stable. Dosage should be stopped, at least in the short term, if patients have severe vomiting and/or diarrhoea as severe gastrointestinal upset may herald lactic acidosis and also acute renal impairment. If the dosage of metformin is continued, the acute renal impairment will lead to excessive accumulation of metformin which may contribute to the lactic acidosis.

Metformin is widely used for the oral treatment of Type 2 diabetes. There is considerable disagreement about its dosage and involvement in the development of lactic acidosis in patients with renal impairment but, before any discussion of these questions, its absorption and elimination should be described.

FIGURE 1. RELATIONSHIP BETWEEN THE RENAL CLEARANCE OF METFORMIN AND CREATININE CLEARANCE. THE DATA WAS OBTAINED FROM SEVERAL PUBLICATIONS.[1] ERRORS BARS (SD) ARE FROM PUBLISHED RESULTS WHERE MEAN CLEARANCES ± SD WERE PRESENTED.



CLINICAL PHARMACOKINETICS OF METFORMIN

Metformin is absorbed incompletely from the gastrointestinal tract, the extent of absorption ranging from about 20 to 80% of the oral dose. The cause of the very considerable variation is not known but may be due to genetic variants of transporters in the gastrointestinal tract, or more likely to variable amounts of transporters in the small intestine.[1]

At least 80% of the absorbed metformin is excreted unchanged in urine. As expected, the renal clearance of metformin decreases with decreasing renal function.[1] *(Fig. 1)* The correlation indicates that the dosage of metformin should be reduced approximately in proportion to decreasing renal function as measured by the eGFR or creatinine clearance. However, there is considerable variation in the correlation between creatinine and metformin clearances. *(Fig. 1)* Adjustments of dosage may be needed depending upon the patient's response to the drug.

The measurement of the plasma concentrations is not standard clinical practice. However, if plasma concentrations are measured, our tentative recommendation is that the mean plasma concentrations over a dosage interval should not exceed 2.5 mg/L.[1] The corresponding peak concentrations should not exceed 5 mg/L during dosage with the sustained release tablets or 4 mg/L during dosage with the immediate release tablets.

METFORMIN AND LACTIC ACIDOSIS

The possible incidence of lactic acidosis during treatment with metformin is of great clinical concern as the death rate approaches 50%. It is diagnosed when a patient has a blood pH<7.35 and plasma lactate concentrations >5.0 mmol/L. Lactic acidosis was associated with the

The use of metformin in diabetic patients with renal impairment ...continued

related drug, phenformin, and was the reason for the withdrawal of this drug. A recent estimation of the incidence of lactic acidosis is 3.3 cases per 100,000 patient years of treatment with metformin.[2] It is of note that lactic acidosis also develops during treatment with the other major group of oral hypoglycaemic drugs, the sulfonylureas, where the incidence of lactic acidosis was estimated as 4.8 per 100,000 patient years. Furthermore, no case of lactic acidosis was recorded in clinical trials on metformin.[3] These trials included studies over more than 70,000 patient-years of metformin treatment but selection to exclude patients with risk factors for lactic acidosis and good patient care is likely to have contributed to the absence of this adverse effect in clinical trials.

Although most authors reporting lactic acidosis during metformin treatment have concluded that metformin was associated with the acidosis, this is not a universal opinion. There is a poor correlation between the plasma concentrations of metformin with both lactate concentrations and mortality.[4] However, as the concentrations of lactate and metformin are changing rapidly[5], the poor correlation is understandable and most likely related to timing of the blood samples.

Although lactic acidosis is clearly uncommon during treatment with metformin, we consider that high concentrations of metformin can contribute to lactic acidosis. Most importantly, massive overdoses taken with suicidal intent have caused lactic acidosis.[6] Furthermore, plasma lactate begins to increase when plasma metformin concentrations are greater than about 20 mg/L (150 µmol/L) in rats[7] and it is notable that plasma concentrations of metformin of greater than 20 mg/L were recorded in about 50% of patients with lactic acidosis associated with metformin.[8]

Various symptoms and risk factors have been noted in patients who have developed lactic acidosis during treatment with metformin (Box). However, hospitalisation for lactic acidosis is generally preceded by severe vomiting and/or diarrhoea. On admission, patients typically are in acute renal failure.4 Because of this observation, it is commonly stated that metformin should only be prescribed if patients' creatinine clearance or eGFR is above a defined low threshold. The problem for prescribers is that the statements on the limit are inconsistent and, furthermore, there is considerable doubt about these recommendations.

The present Product Information (label) on metformin contains statements, such as: "Life threatening lactic acidosis can occur due to accumulation of metformin. The main risk factor is renal impairment. Other risk factors include old age associated with reduced renal function and high doses of metformin above 2 g/day." The product information also contains the statement that metformin should not be prescribed in patients with GFR values below 60 mL/min. The Australian Medicine Handbook lists a lower threshold of 30 mL/min.[9]

The National Institute for Health and Clinical Excellence (NICE)[10] has more detailed recommendations and comments:

- Review the dose of metformin if the serum creatinine exceeds 130 micromol/litre or the estimated glomerular filtration rate (eGFR) is below 45 ml/minute/1.73-m^2.
- Stop the metformin if the serum creatinine exceeds 150 micromol/litre or the eGFR is below 30 ml/minute/1.73-m^2.
- Prescribe metformin with caution for those at risk of a sudden deterioration in kidney function and those at

BOX – THE SAFE USE OF METFORMIN IN RENAL IMPAIRMENT

Dosage

- The maximal dosage of metformin should be 3 g daily in patients with good renal function and reduced in line with the estimated eGFR or creatinine clearance. For example, a patient with an estimated clearance of 60 ml/min should initially be prescribed 1.5 g daily and increased only if the response is inadequate and the drug is well tolerated.
- Metformin may be used in patients with eGFR or creatinine clearances down to 30 mL/min provided that renal function is stable.
- The initial dosage should not be based on the plasma creatinine although changes in renal function can be checked by plasma creatinine

Precautions

- Patients should stop metformin immediately and call their medical practitioner if they have severe vomiting and/or diarrhoea.
- Metformin should be used with caution in any patient who is at risk of a sudden deterioration in kidney function.

risk of eGFR falling below 45 ml/minute/1.73-m^2.

The practicality is that metformin is commonly prescribed for patients with estimated glomerular filtration rates down to 30 mL/min[11] and, in small numbers of patients, with substantial renal impairment ((eGFR < 30 mL/min)[12] apparently without them becoming acidotic. In a recent study, we have also administered metformin to patients with creatinine clearances ranging from 15 to 35 mL/min for 6 weeks. No case of lactic acidosis developed. On the other hand, it has been claimed that lactic acidosis associated with metformin can occur in patients with previously normal renal function.[5]

CONCLUSIONS

It now appears that patients, even those with substantially reduced renal function, can take metformin for prolonged periods without the development of lactic acidosis but, in occasional patients, there is a trigger for the development of this acidosis. The first symptom indicating a significant problem is often prolonged vomiting and/or diarrhoea leading to dehydration and impaired renal function as well as accumulation of metformin if its dosage is continued.[1] The product literature does note that dehydration and gastrointestinal disturbances are precautions to the use of metformin but we consider that severe vomiting and/or diarrhoea is not emphasized sufficiently as a herald of lactic acidosis. *(See Box)* Elderly patients taking diuretics during hot summer months pose a risk for dehydration and metformin toxicity. The NICE document[10] should also be amended to emphasise this problem.

No conflict of interest declared.

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KEY PRACTICE POINTS

- Renal impairment Creatinine Clearance <30 mL/min or GFR <45 ml/minute/1.73m^2 warrants caution and dose reduction
- Both metformin and sulphonylureas can cause lactic acidosis
- Warning signs are vomiting, diarrhoea, dehydration and acute renal failure
- Beware of elderly patients on diuretics & metformin and check renal function regularly

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