Why is metformin contraindicated in chronic kidney disease?

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TO THE EDITOR: In their article about the care of patients with advanced chronic kidney disease, Sakhuja et al[1] mentioned that metformin is contraindicated in chronic kidney disease.

Metformin is a good and useful drug. Not only is it one of the cheapest antidiabetic medications, it is the only one shown to reduce cardiovascular mortality rates in type 2 diabetes mellitus.

Although metformin is thought to increase the risk of lactic acidosis, a Cochrane review[2] found that the incidence of lactic acidosis was only 4.3 cases per 100,000 patient-years in patients taking metformin, compared with 5.4 cases per 100,000 patient-years in patients not taking metformin. Furthermore, in a large registry of patients with type 2 diabetes and atherothrombosis,[3] the rate of all-cause mortality was 24% lower in metformin users than in nonusers, and in those who had moderate renal impairment (creatinine clearance 30–59 mL/min/1.73 m^2) the difference was 36%.[3]

A trial by Rachmani et al[4] raised questions about the standard contraindications to metformin. The authors reviewed 393 patients who had at least one contraindication to metformin but who were receiving it anyway. Their serum creatinine levels ranged from 1.5 to 2.5 mg/dL. There were no cases of lactic acidosis reported. The patients were then randomized either to continue taking metformin or to stop taking it. At 2 years, the group that had stopped taking it had gained more weight, and their glycemic control was worse.

In the Cochrane analysis,[2] although individual creatinine levels were not available, 53% of the studies reviewed did not exclude patients with serum creatinine levels higher than 1.5 mg/dL. This equated to 37,360 patient-years of metformin use in studies that included patients with chronic kidney disease, and did not lead to lactic acidosis.

Even though metformin's US package insert says that it is contraindicated if the serum creatinine level is 1.5 mg/dL or higher in men or 1.4 mg/dL or higher in women or if the creatinine clearance is "abnormal," in view of the available evidence, many countries (eg, the United Kingdom, Australia, the Netherlands) now allow metformin to be used in patients with glomerular filtration rates as low as 30 mL/min/1.73m^2, with lower doses if the glomerular filtration rate is lower than 45.[5]

The current contraindication to metformin in chronic kidney disease needs to be reviewed. In poor countries like India, this cheap medicine may be the only option available for treating type 2 diabetes mellitus, and it remains the first-line therapy for type 2 diabetes mellitus as recommended by the International Diabetes Federation, the American Diabetes Association, and the European Association for the Study of Diabetes.[5]

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IN REPLY: We appreciate Dr. Imam's comments regarding using metformin in those with chronic kidney disease.

The US Food and Drug Administration currently lists metformin as contraindicated in those with mild to moderate renal insufficiency, with serum creatinine levels greater than or equal to 1.5 mg/dL in males and greater than or equal to 1.4 mg/dL in females. This contraindication is based on the pharmacokinetics of the medication and, likely, the association of a similar medication, phenformin, with lactic acidosis, which eventually led to its withdrawal from the market. However, lactic acidosis is much less frequent with metformin than with phenformin.[1]

We agree that metformin is an invaluable medication for diabetes mellitus not requiring insulin. We also agree that lactic acidosis is rare, especially in those with mild renal insufficiency. However, lactic acidosis does occur in patients with chronic kidney disease while on metformin and, however rare, when it does occur it is a life-threatening event.[2]

The clearance of metformin is strongly dependent on kidney function,[3] and therefore guidelines still recommend reducing the dose in those with moderate renal insufficiency and recommend considering stopping the medication in those with severe renal insufficiency—the population we were talking about in our article.[4] We are aware of changes to the guidelines that have been made by various groups, and in many circumstances we ourselves take an individualized approach, weighing the risks and benefits of continued therapy with the patient and his or her primary care provider. That being said, we did not believe that such nuanced recommendations were appropriate for our article, especially since they are contrary to marketing restrictions for the drug.

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