

Old Age May Not Be a Contraindication to the Use of Metformin

Harn-Shen Chen*

*Division of Endocrinology and Metabolism, Department of Medicine, Taipei Veterans General Hospital, and
Department of Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan, R.O.C.*

The antihyperglycemic action of metformin is based on suppression of endogenous glucose production in patients with type 2 diabetes. Metformin has been used as a glucose-lowering agent in type 2 diabetes since 1957, but was withdrawn from the United States in 1975.¹ This was largely due to the historical experience of lactic acidosis with phenformin, another biguanide. Lactic acidosis, characterized by the presence of metabolic acidosis and elevated lactate levels, is a nonspecific end-stage consequence of a variety of serious disorders characterized by tissue hypoxia, particularly conditions such as septicemia, renal or hepatic failure. Lactic acidosis has also been reported in patients treated with metformin; however, these patients were mostly elderly and had multiple comorbidities. In contrast to the earlier biguanides, phenformin and buformin, which have a half-life of 7–12 hours, metformin has a half-life of only 1.5–5.0 hours, is less lipophilic, does not accumulate in the liver and is eliminated unchanged by glomerular filtration and tubular secretion. In May 1995, metformin was approved in the United States and rapidly gained wide acceptance. The efficacy and benefits of metformin treatment in type 2 diabetes have been confirmed by recent large-scale studies (United Kingdom Prospective Diabetes Study) and endorsed by many consensus statements.^{2,3} However, a large list of contraindications may increase the incidence of lactic acidosis, which precludes millions of patients with type 2 diabetes from taking metformin. Such contraindications include renal impairment, cardiac insufficiency and old age, and immediately receive intravenous contrast medium.

From the time when metformin was re-introduced in the United States through to June 30, 1996, the Food and Drug Administration has received reports of lactic acidosis in 66 patients treated with this drug.⁴

In 47 patients, the diagnosis was confirmed on the basis of circulating lactate values, in accordance with established criteria for the diagnosis of lactic acidosis. On the basis of the estimate that 1 million Americans are taking metformin, the reported rate of confirmed lactic acidosis should be about 5 cases per 100,000 patient-years. Of the 47 patients with confirmed diagnosis, 8 patients (17%) were older than 80 years. The subsequently approved label stated that metformin treatment should not be initiated in patients aged >80 years unless their creatinine clearance is normal. A recent meta-analysis pooling data from 274 comparative trials and cohort studies revealed no cases of fatal or nonfatal lactic acidosis in 59,321 patient-years of metformin use or in 51,627 patient-years in the non-metformin group.⁵ Using Poisson statistics, the upper limit for the true incidence of lactic acidosis per 100,000 patient-years was 5.1 cases in the metformin group and 5.8 cases in the non-metformin group. There was no difference in lactate levels, either as mean treatment levels or as a net change from baseline, for metformin compared to non-metformin therapies.

Taken together, the available evidence indicates that the incidence of lactic acidosis in type 2 diabetic patients treated with metformin is similar to that in patients who do not receive metformin. But old age and other comorbidities could increase the risk of lactic acidosis. The question arises as to whether old age *per se* is a contraindication to the use of metformin. In this issue of the *Journal of the Chinese Medical Association*, Lin et al⁶ assessed fasting plasma lactate levels in ambulatory elderly Taiwanese patients aged >80 years with type 2 diabetes taking metformin to identify independent risk factors for hyperlactemia in these patients. They recruited 66 elderly and 79 younger type 2 diabetes patients receiving metformin therapy. They



*Correspondence to: Dr Harn-Shen Chen, Division of Endocrinology and Metabolism, Department of Medicine, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, R.O.C.
E-mail: chenhs@vghtpe.gov.tw • Received: September 14, 2010 • Accepted: November 1, 2010

found that plasma lactate concentrations in ambulatory elderly type 2 diabetic patients with metformin therapy were not different from those in the younger group. They concluded that old age *per se* should not preclude prescription of metformin for the treatment of type 2 diabetes.

Some studies of patients with type 2 diabetes, including those over 70 years of age, have shown that metformin treatment is not associated with significantly increased plasma lactate levels.⁷ It is important to point out that patients with contraindications were excluded from many studies examining the effects of metformin on plasma lactate. Dr Lin's group presented 2 groups of type 2 diabetes patients with differences not only in age but also in creatinine clearance rate, and found that both groups had the same concentration of plasma lactate. Although there were some limitations in their study, they have provided preliminary data to show that old age *per se* cannot increase plasma lactate in type 2 diabetes patients treated with metformin.

Most patients with type 2 diabetes are over 65 years old, and there is no evidence that old age should, in itself, be a reason to withhold metformin. Metformin is undoubtedly contraindicated in patients with severe renal impairment. Evidence from meta-analyses suggest that metformin can be used safely in chronic renal insufficiency with a creatinine level up to 1.5 mg/dL.⁸ It must be borne in mind, however, that serum creatinine generally overestimates renal function, particularly in the elderly and in those with reduced muscle mass. Therefore, calculation of creatinine clearance according to the method of Cockcroft-Gault or estimation of the glomerular filtration rate is preferable.

In conclusion, an estimated glomerular filtration rate <40 mL/min, but not old age *per se*, may be an acceptable contraindication to the use of metformin. Therefore, I suggest that metformin could be prescribed for patients older than 80 years of age who have normal renal function and no other contraindications.

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