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Metformin-Associated Lactic Acidosis

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Metformin has been used in Europe since the 1970s to treat type 2 diabetes mellitus (T2DM). Usage has increased since the results of the UK Prospective Diabetes Study were published [1]. Metformin is widely endorsed as initial therapy by professional organizations because of low cost, a good safety profile, and potential protection against cardiovascular disease [2]. Therefore, it is now considered to be the first-choice oral treatment for T2DM patients in the absence of contraindications [2]. However, concerns about the risk of lactic acidosis (LA) delayed the introduction of metformin into clinical practice in the USA until 1995, and such concerns persist [3]. The predecessor of metformin, the biguanide phenformin, clearly causes LA, and it has been suggested that metformin has been judged "guilty by association" [4]. The incidence of LA is 10- to 20-fold less in patients who receive metformin than phenformin [5]. Indeed, one report concluded that there was no consistent link between metformin therapy and LA [6]. The most common side-effects of metformin are gastrointestinal disturbances, including anorexia, nausea, abdominal discomfort, and diarrhea. These mild symptoms are usually reversed after discontinuation or dose reduction. The incidence of LA in patients on metformin therapy appears to be extremely low, but LA can be fatal when it occurs [7]. A rare but serious condition termed metformin-associated lactic acidosis (MALA) can develop in patients with predisposing factors such as renal impairment, hepatic disease, congestive heart failure, or sepsis [8].

Kim and colleagues [9] investigated the clinical profiles of MALA patients and risk factors for MALA, and analyzed treatment modalities by survival in a single hospital. Although a few study limitations were evident (e.g., lack of data on serum metformin levels, and a small sample size), the analysis afforded three important insights. First, most patients who presented with MALA exhibited impaired renal function on admission, with or without other precipitating conditions. As metformin is excreted unmetabolized in the urine [10], impairment of renal function resulted in metformin accumulation in plasma, in turn causing LA. Second, age was the most important prognostic factor; neither metformin dose nor its pH was of prognostic value. Third, mortality was lower than that reported in other studies that have evaluated patients with similar forms of acidosis. Early renal replacement therapy was initiated in four of their seven patients. This therapy corrects acidosis by filtering out anions, and efficiently removes metformin from plasma. Another previous study found that prompt recognition of LA and early treatment via bicarbonate dialysis can yield favorable clinical outcomes [11]. In conclusion, early recognition of risk factors for MALA, with prompt initiation of renal replacement therapy, improves survival. The most recent review by Kajbaf and Lalau [12] found that the overall mortality rate from MALA was around 50% during 1960 to 2000 but has since fallen to about 25%. However, metformin therapy was contraindicated (relatively or absolutely) in six of the seven patients reported by Kim et al. [9]. Therefore, risk factors for MALA should be carefully assessed, and renal function monitored, to prevent MALA in patients who are taking metformin.

An Italian national 10-year survey on MALA has recently

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been published [13]. This systemic nationwide research identified risk factors for, and initial symptoms/signs of, MALA. It would be beneficial to conduct such a survey in Korea to develop optimal management strategies. Then risk-minimization measures could be taken at a national level to prevent this serious complication. Until that happens, metformin use by elderly patients with mild to moderate chronic kidney disease should feature appropriate dose reductions and careful follow-up of kidney function.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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