SUBMITTED TO EVIDENCE-BASED MEDICINE

Category: Therapeutics

Study type: Systematic review

Author's declarative title : Time for reappraisal of contra-indications of metformin use in patients with type 2 diabetes and mild to moderate renal impairment

Citation: Inzucchi SE, Lipska KJ, Mayo H, Bailey CJ, McGuire DK. Metformin in patients with type 2 diabetes and kidney disease: a systematic review. JAMA. 2014;312(24):2668-75.

Commentary (799 words starting from context including references)

Context

Metformin is considered as the best initial pharmacological option to lower glucose concentrations in patients with type 2 diabetes mellitus (T2DM).[1] As metformin may be combined with any other glucose-lowering therapy, a large majority of patients may receive metformin.[1] However, because the drug is cleared by the kidneys, it may accumulate when renal function decreases, with the potential for exposure-dependent toxicity that could precipitate lactate accumulation.

Chronic kidney disease (CKD) is a frequent scenario in T2DM, a condition that may challenge the use of many glucose-lowering agents.[2] There is increasing evidence that the current cut-off points for renal safety of metformin in the U.S. may be overly restrictive.[3] Consequently, a substantial number of patients may be deprived of using metformin although the drug might be beneficial to them.[4]

This systematic review examines the risk of metformin-associated lactic acidosis (MALA) in individuals with CKD.

Methods

This review searched the MEDLINE and Cochrane databases for English-language articles pertaining to metformin, CKD, and lactic acidosis in humans between 1950 and June 2014. Of an original 818 articles, 65 were finally examined, including pharmacokinetic/metabolic studies [10], case series [20], cross-sectional, observational, and pharmacosurveillance studies [31], meta-analyses [3], and one clinical trial [1].

Findings

Although metformin clearance is decreased in CKD, drug levels, even slightly increased, remain within therapeutic range when glomerular filtration rate (GFR) is greater than 30 mL/min per 1.73 m^2 and circulating lactate levels are not substantially increased when metformin is used in patients with reduced GFR.

Several observational studies have explored the relationship between metformin and lactic acidosis and no consistent link between metformin use and occurrence of lactic acidosis has been found. The frequency of lactic acidosis in the setting of metformin therapy is very low and numerically similar to what appears to be the background rate in the population with T2DM.

A conservative synthesis of these data is that, as long as kidney function is stable and the patient is observed closely, metformin is unlikely to measurably increase the risk of lactic acidosis in T2DM patients with mild to moderate CKD (GFR 30-60 mL/min per 1.73 m^2).

Commentary

It is difficult to make firm conclusions from observational or pharmacosurveillance studies about metformin and lactic acidosis in patients with CKD.[5] There have been no randomized clinical trials to test the specific hypothesis that metformin is safe in patients with mild to moderate CKD.[2] Randomized trials would help to better inform evidence-based guidelines. However, given the rarity of lactic acidosis in the setting of metformin therapy,[6] a study that would demonstrate metformin non-inferiority compared with other agents is clearly impracticable. Thus, well documented national patient registries might be a reasonable alternative.

Despite the fact that current regulatory cautions to avoid metformin in patients with mild to moderate CKD apparently are not consistently being followed in real-world practice, lactic acidosis developed rarely and, when it occurred, was considered primarily related to underlying disease rather than to metformin.[5]

In conclusion, this review supports consideration of a change to metformin's prescribing guidelines, with cautious use allowed in patients with mild to moderate CKD, as already accepted in many less restrictive policy revisions outside the United States[1-3,7].

Implications for practice

Any new expansion of metformin use in patients with mild to moderate CKD will need to be accompanied by appropriate dosage reductions (although not validated in a clinical trial !) and careful regular follow-up assessments of kidney function.[1] If metformin is given in such patients, clear-cut instruction to stop metformin in any situation able to provoke dehydration or acute renal dysfunction is mandatory.[8]

References

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Competing interest: none