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[Intervention Review]

Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus

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ABSTRACT

Background

Metformin is an oral anti-hyperglycemic agent that has been shown to reduce total mortality compared to other anti-hyperglycemic agents, in the treatment of type 2 diabetes mellitus. Metformin, however, is thought to increase the risk of lactic acidosis, and has been considered to be contraindicated in many chronic hypoxemic conditions that may be associated with lactic acidosis, such as cardiovascular, renal, hepatic and pulmonary disease, and advancing age.

Objectives

To assess the incidence of fatal and nonfatal lactic acidosis, and to evaluate blood lactate levels, for those on metformin treatment compared to placebo or non-metformin therapies.

Search methods

A comprehensive search was performed of electronic databases to identify studies of metformin treatment. The search was augmented by scanning references of identified articles, and by contacting principal investigators.

Selection criteria

Prospective trials and observational cohort studies in patients with type 2 diabetes of least one month duration were included if they evaluated metformin, alone or in combination with other treatments, compared to placebo or any other glucose-lowering therapy.

Data collection and analysis

The incidence of fatal and nonfatal lactic acidosis was recorded as cases per patient-years, for metformin treatment and for non-metformin treatments. The upper limit for the true incidence of cases was calculated using Poisson statistics. In a second analysis lactate levels were measured as a net change from baseline or as mean treatment values (basal and stimulated by food or exercise) for treatment and comparison groups. The pooled results were recorded as a weighted mean difference (WMD) in mmol/L, using the fixed-effect model for continuous data.

Main results

Pooled data from 347 comparative trials and cohort studies revealed no cases of fatal or nonfatal lactic acidosis in 70,490 patient-years of metformin use or in 55,451 patients-years in the non-metformin group. Using Poisson statistics the upper limit for the true incidence of lactic acidosis per 100,000 patient-years was 4.3 cases in the metformin group and 5.4 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.

Authors' conclusions

There is no evidence from prospective comparative trials or from observational cohort studies that metformin is associated with an increased risk of lactic acidosis, or with increased levels of lactate, compared to other anti-hyperglycemic treatments.

PLAIN LANGUAGE SUMMARY**Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus**

Metformin, a medication used to lower glucose levels in patients with diabetes mellitus, has long been thought to increase the risk for a metabolic disorder known as lactic acidosis. This review summarised data from all known comparative and observational studies lasting at least one month, and found no cases of fatal or nonfatal lactic acidosis in 70,490 patient-years of metformin use, or in 55,451 patient-years for those not on metformin. Average lactate levels measured during metformin treatment were no different than for placebo or for other medications used to treat diabetes. In summary, there is no evidence at present that metformin is associated with an increased risk for lactic acidosis when prescribed under the study conditions.