Review: Metformin does not increase risk for lactic acidosis or increase lactate levels in type 2 diabetes

Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. **Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus: systematic review and meta-analysis.** Arch Intern Med. 2003;163:2594-602.

QUESTIONS

In patients with type 2 diabetes mellitus, what is the risk for fatal and nonfatal lactic acidosis associated with metformin compared with placebo or other glucose-lowering therapies? Does metformin increase lactate levels?

DATA SOURCES

A previous review was updated. Studies were identified by searching (up to March 2002) the Cochrane Library, MEDLINE, Reactions, and EMBASE/Excerpta Medica; scanning the references of identified articles and reviews; reviewing the abstracts of clinical conferences; and contacting the authors of relevant studies and manufacturers of metformin.

STUDY SELECTION AND ASSESSMENT

Studies were selected if they were randomized controlled trials (RCTs) or cohort studies ≥ 1 month in duration that compared metformin, alone or in combination with other treatments, with placebo or another glycemic-lowering intervention for type 2 diabetes. Methodological quality was assessed using criteria that considered randomization procedure, blinding, and withdrawals and dropouts.

OUTCOMES

Fatal lactic acidosis, nonfatal lactic acidosis, and blood lactate levels for metformin compared with placebo or other nonbiguanide therapies, and for metformin compared with phenformin.

MAIN RESULTS

194 studies (126 RCTs and 68 cohort studies, *n* = 56 692, mean age 57 y, 61% men) met the selection criteria. Mean trial duration was 2.1 years. Metformin was administered in daily doses of 1 to 3 g and was titrated clinically. Nonbiguanide comparison treatments included placebo, diet, insulin, glyburide, gliclazide, glipizide, glibenclamide, glimepiride, chlorpropamide, tolbutamide, acarbose, nateglinide, repaglinide, miglitol, troglitazone, rosiglitazone maleate, and guar gum. 44% of the trials allowed for the inclusion of patients with renal insufficiency, or did not explicitly exclude them. No cases of fatal or nonfatal lactic acidosis were reported in any of the included studies. Poisson statistics with 95% confidence intervals showed the probable upper limit for the true incidence of lactic acidosis in the metformin and comparison groups was 8.1 and 9.9 cases per 100 000 patient-years, respectively. Groups did not differ for the change from baseline in lactate levels (weighted mean difference [WMD] 0.11 mmol/L, 95% CI −0.01 to 0.24). During treatment, the metformin and comparison groups did not differ in mean lactate levels (WMD 0.06 mmol/L, CI 0 to 0.1). By contrast, mean lactate levels were lower in patients who received metformin than in those who received phenformin (WMD −0.8 mmol/L, CI −0.9 to −0.6).

CONCLUSION

In patients with type 2 diabetes mellitus, metformin is not associated with an increased risk for lactic acidosis or with an increase in lactate levels.

Source of funding: No external funding.

For correspondence: Dr. S.R. Salpeter, Santa Clara Valley Medical Center, San Jose, CA, USA. E-mail salpeter@stanford.edu.

COMMENTARY

Since its introduction in the United States in 1995, the biguanide drug metformin has been widely prescribed as an effective oral antihyperglycemic drug for the treatment of diabetes mellitus. Its predecessor, phenformin, was removed from the U.S. market in the 1970s because of its association with lactic acidosis. Based on several case reports and prescribing statistics, the incidence of this adverse effect from metformin has been estimated to be about 3 per 100 000 patient-years, with an estimated fatality rate of approximately 50%. Identified risk factors for biguanide-associated lactic acidosis include renal or hepatic insufficiency, heart failure, shock, acidosis, and diseases or clinical situations predisposing to these disorders (1).

The meta-analysis by Salpeter and colleagues encompassed nearly 37 000 patient-years of metformin treatment from reported studies and did not find a single case of lactic acidosis. Statistically, this is not inconsistent with previous estimates. Moreover, it is highly likely that in the context of controlled clinical trials, patients with absolute contraindications would be excluded. On the other hand, several reports have documented that outside of clinical trials metformin is commonly prescribed to patients with absolute contraindications that place them at risk for metformin-associated lactic acidosis (2, 3).

An important caveat to the conclusions made by Salpeter and colleagues is that the lack of evidence of an association between metformin and lactic acidosis is predicated on the proviso that the drug is prescribed under clinical trial conditions, taking contraindications into account.

James A. Kruse, MD
Wayne State University School of Medicine
Detroit, Michigan, USA

References

1. **Kruse JA.** Metformin-associated lactic acidosis. J Emerg Med. 2001;20:267-72.
2. **Horlen C, Malone R, Bryant B, et al.** Frequency of inappropriate metformin prescriptions [Letter]. JAMA. 2002;287:2504-5.
3. **Calabrese AT, Coley KC, DaPos SV, Swanson D, Rao RH.** Evaluation of prescribing practices: risk of lactic acidosis with metformin therapy. Arch Intern Med. 2002;162:434-7.