Review: metformin does not increase risk of lactic acidosis or increase lactate levels in type 2 diabetes

Salpeter SR, Greyber E, Pasternak GA, *et al.* 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.

Clinical impact ratings GP/FP/Primary care ★★★★★☆ IM/Ambulatory care ★★★★★☆ Internal medicine ★★★★★☆ Endocrine ★★★★★☆

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

METHODS

Data sources: the Cochrane Library, Medline, Reactions, and EMBASE/Excerpta Medica (up to March 2002); references of identified articles and reviews; abstracts of clinical conferences; and authors of relevant studies and manufacturers of metformin.

Study selection and assessment: randomised controlled trials (RCTs) or cohort studies ≥1 month in duration that compared metformin, alone or in combination in other treatments, with placebo or another glycaemic lowering intervention for type 2 diabetes. Methodological quality was assessed using criteria that considered randomisation procedure, blinding, and withdrawals and dropouts.

Outcomes: fatal lactic acidosis, non-fatal lactic acidosis, and blood lactate levels for metformin compared with placebo or other non-biguanide 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 1–3 g and was titrated clinically. Non-biguanide 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 non-fatal 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 of lactic acidosis or with an increase in lactate levels.

Abstract and commentary also appear in ACP Journal Club.

Commentary

Since its introduction in the US in 1995, the biguanide drug metformin has been widely prescribed as an effective oral antihyperglycaemic drug for the treatment of diabetes mellitus. Its predecessor, phenformin, was removed from the US 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 *et al* 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 metformin is commonly prescribed outside of clinical trials to patients with absolute contraindications that place them at risk of metformin associated lactic acidosis.^{2,3}

An important caveat to the conclusions made by Salpeter *et al* 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.

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- 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, *et al.* Evaluation of prescribing practices: risk of lactic acidosis with metformin therapy. *Arch Intern Med* 2002;**162**:434–7.

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