Review: Metformin does not increase fatal or nonfatal lactic acidosis or blood lactate levels in type 2 diabetes mellitus

Salpeter S, Greyber E, Pasternak G, Salpeter E. **Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus.** Cochrane Database Syst Rev. 2002(2):CD002967 (latest version 27 Feb 2002).

QUESTION

In patients with type 2 diabetes mellitus, does metformin increase the risk for fatal and nonfatal lactic acidosis or increase blood lactate levels compared with placebo or other hypoglycemic therapies?

DATA SOURCES

Studies were identified by searching the Cochrane Library (to April 2000), MEDLINE (1966 to 2000), EMBASE/Excerpta Medica (1974 to 2000), Oldmedline, Reactions (1983 to May 2000), Index Medicus (1959 to 1965), and bibliographies of identified papers and by contacting investigators.

STUDY SELECTION

Clinical trials and cohort studies were selected if they included patients with type 2 diabetes, lasted ≥ 1 month, compared metformin alone or combined with other treatments with placebo or any other hypoglycemic therapy, and reported the number of patients and duration of treatment.

DATA EXTRACTION

Data were extracted on study methods and quality, participants, interventions, and outcomes. Attempts were made to contact authors for missing data.

MAIN RESULTS

176 studies (118 prospective comparative trials, 46 prospective cohort studies, and 12 retrospective cohort studies; mean study duration 2.1 y, mean drop-out rate 9.2%) met the selection criteria. 26 099 participants (mean age 57 y, 61% men) were followed for 65 621 patient-years (17 156 participants [35 619 patient-y] in the metformin group and 8943 participants [30 002 patient-y] in the nonmetformin group). 92 studies were randomized trials, 25 were nonrandomized trials, and 58 were cohort studies. Metformin was given in doses of 1 to 3 g/d. Comparisons included placebo, diet, insulin, glyburide, gliclazide, glipizide, glibenclamide, glimiperide, chlorpropramide, tolbutamide, acarbose, nateglinide, repaglinide, miglitol, troglitazone, rosiglitazone, and guar gum.

Pooled results from the 176 studies showed no occurrences of fatal or nonfatal lactic acidosis in the metformin or nonmetformin groups. Metformin and placebo or other nonbiguanide therapies did not differ for mean change from baseline in blood lactate levels (weighted mean difference [WMD] 0.12 mmol/L, 95% CI −0.01 to 0.25 mmol/L; fixed-effects model). Mean blood lactate levels during treatment were lower for metformin than for phenformin (WMD −0.75 mmol/L, CI −0.86 to −0.65 mmol/L; fixed-effects model).

CONCLUSION

In patients with type 2 diabetes mellitus, metformin does not increase the risk for fatal or nonfatal lactic acidosis or increase blood lactate levels compared with placebo or other hypoglycemic therapies.

Source of funding: Not stated.

For correspondence: Dr. S. Salpeter, Stanford University and Santa Clara Valley Medical Center, San Jose, CA, USA. E-mail shelley.salpeter@hhs.co.santa-clara.ca.us.

COMMENTARY

Metformin improves glycemic control in type 2 diabetes without causing weight gain or hypoglycemia and is the only oral hypoglycemic drug that has reduced cardiovascular morbidity and mortality in a randomized trial (1). However, metformin might increase the risk for lactic acidosis. For this reason, many prescribing guidelines suggest that metformin be contraindicated in patients at higher-than-average risk for lactic acidosis.

Salpeter and colleagues hoped to compare the incidence of lactic acidosis in metformin users with those taking other medications or placebo, but this proved impossible because not a single case of lactic acidosis was found in any of these studies. Although many of the included studies did not specifically exclude persons with renal, hepatic, cardiac, or pulmonary disease, it is possible that not enough persons with these comorbid conditions were enrolled in the studies to allow accurate risk estimates. In Saskatchewan, where comprehensive, linkable databases of prescriptions and health care encounters are maintained, only 2 cases of lactic acidosis were found among 11 797 persons who filled metformin prescriptions over a 15-year period (9 cases/100 000 patient-y) (2). This risk is strikingly similar to the lactic acidosis rate of 9.7/100 000 patient-years in a large U.S. Health Maintenance Organization in 1993 to 1994, when metformin was not yet available in the United States (3). Because > 25% of persons receiving metformin have ≥ 1 "absolute" contraindication to it (4), the low observed risk for lactic acidosis in metformin users cannot be attributed solely to "prudent" prescribing. In contrast to phenformin, no credible evidence exists that metformin increases the risk for lactic acidosis beyond what would be expected from underlying diseases. It is possible that overly restrictive contraindications to metformin might result in many persons being denied an excellent drug while preventing few if any cases of lactic acidosis.

Ronald J. Sigal, MD, MPH
Ottawa Health Research Institute
Ottawa, Ontario, Canada

References

1. **UK Prospective Diabetes Study (UKPDS) Group.** Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998;352:854-65.
2. **Stang M, Wysowski DK, Butler-Jones D.** Incidence of lactic acidosis in metformin users. Diabetes Care. 1999;22:925-7.
3. **Brown JB, Pedula K, Barzilay J, Herson MK, Latare P.** Lactic acidosis rates in type 2 diabetes. Diabetes Care. 1998;21:1659-63.
4. **Emslie-Smith AM, Boyle DI, Evans JM, Sullivan F, Morris AD.** Contraindications to metformin therapy in patients with type 2 diabetes—a population-based study of adherence to prescribing guidelines. Diabet Med. 2001;18:483-8.