Cochrane for Clinicians

Putting Evidence into Practice

Does Metformin Increase the Risk of Fatal or Nonfatal Lactic Acidosis?

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The Cochrane Abstract on the next page is a summary of a review from the Cochrane Library. It is accompanied by an interpretation that will help clinicians put evidence into practice. Dr. Cayley presents a clinical scenario and question based on the Cochrane Abstract, followed by an evidence-based answer and a critique of the review. The practice recommendations in this activity are available at http://www.cochrane.org/reviews/en/ab002967.html.

EB CME

This clinical content conforms to AAFP criteria for evidence-based continuing medical education (EB CME). See CME Quiz on page 1065.

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A collection of Cochrane for Clinicians published in *AFP* is available at http://www.aafp.org/afp/cochrane.

Clinical Scenario

A 70-year-old woman with type 2 diabetes mellitus who is in otherwise good health is experiencing gradually increasing glucose levels. Her physician considers starting her on an oral diabetes agent, but is concerned that her age may put her at risk for adverse effects if she is treated with metformin (Glucophage).

Clinical Question

Does metformin increase the risk of fatal or nonfatal lactic acidosis?

Evidence-Based Answer

In patients without standard contraindications to metformin therapy, metformin does not increase the risk of lactic acidosis.[1] (Strength of Recommendation = B, based on inconsistent or limited-quality patient-oriented evidence)

Practice Pointers

The first-line treatments recommended for type 2 diabetes are lifestyle changes and metformin, which is a biguanide antihyperglycemic agent.[2] Demonstrated benefits of metformin include lower cardiovascular mortality than other oral diabetes medications[3] and a reduced risk of death or myocardial infarction in overweight patients with type 2 diabetes.[4] However, because an earlier biguanide, phenformin, was removed from the market after being linked to several cases of lactic acidosis, there have been concerns that metformin may predispose patients to lactic acidosis as well. In light of this, metformin is considered contraindicated in patients with chronic renal insufficiency, pulmonary disease, or hypoxic conditions; abnormal hepatic function; peripheral vascular disease; and in those older than 65 years. The use of metformin in patients with heart failure continues to be controversial.[1]

The authors of this Cochrane review found no cases of fatal or nonfatal lactic acidosis in 347 prospective trials and cohort studies with more than 70,490 patient-years of metformin use.[1] Although the presence or absence of metformin contraindications among participants was not addressed in all studies, the authors note that 97 percent of the studies allowed for at least one metformin contraindication among included patients, and that 26 percent of all participants were estimated to be older than 65 years. Furthermore, one trial specifically studied 393 patients with at least one contraindication to metformin and found no cases of lactic acidosis. All patients in this trial had serum creatinine values ranging from 1.5 to 2.5 mg per dL (132.60 to 221.00 μmol per L).[5]

Because metformin has demonstrated benefits for patient-oriented outcomes in the treatment of type 2 diabetes, the absence of any cases of lactic acidosis among all patients included in the reviewed studies is reassuring regarding the safety of metformin in general. Considering that there was no standardized reporting across the studies of metformin use in the presence of contraindications, definitive conclusions about the safety of metformin in the presence of contraindications are not possible.

Nevertheless, the review authors suggest that concerns for lactic acidosis with metformin use may be overstated for the following three reasons. First, despite chemical similarities, phenformin and metformin have different mechanisms of action. Whereas phenformin can impair hepatic oxidative phosphorylation and increase anaerobic

Cochrane Abstract

Background: Metformin is an oral antihyperglycemic agent that has been shown to reduce total mortality compared with other antihyperglycemic 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 diseases, 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 with placebo or non-metformin therapies.

Search Strategy: 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 at least one month's duration were included if they evaluated metformin, alone or in combination with other treatments, compared with 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 in mmol per 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 patient-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 with 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 with other antihyperglycemic treatments.

lactate production, metformin inhibits hepatic gluconeogenesis without affecting lactate turnover. Second, the case reports of lactic acidosis with metformin use all occurred in patients with other underlying conditions that could independently predispose to lactic acidosis. Third, diabetes alone is a predisposing factor for the development of lactic acidosis; thus, cases of lactic acidosis in patients taking metformin may have been caused by having diabetes rather than by taking metformin.[1]

The reality of current clinical practice is that 54 to 73 percent of patients taking metformin have at least one standard contraindication to its use, and the review authors note that strict adherence to recommended contraindication guidelines would reduce the number of patients with diabetes being treated with metformin by about one half.[1] Because metformin has clear patient-oriented benefits and no demonstrable risk of lactic acidosis in low-risk patients, it should remain a first-line treatment option for patients with type 2 diabetes. Patients with contraindications to metformin may also be those who potentially stand to benefit the most from metformin therapy. Although this Cochrane review does not specifically address the safety of metformin in the presence of contraindications, it suggests that even in the presence of one contraindication, the benefits of metformin use may outweigh the risks.

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REFERENCES

1. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2010;(1):CD002967.

2. Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care.* 2009;32(1):193-203.
3. Selvin E, Bolen S, Yeh HC, et al. Cardiovascular outcomes in trials of oral diabetes medications: a systematic review. *Arch Intern Med.* 2008;168(19):2070-2080.
4. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group [published correction appears in *Lancet.* 1998;352(9139):1558]. *Lancet.* 1998;352(9131):854-865.
5. Rachmani R, Slavachevski I, Levi Z, Zadok B, Kedar Y, Ravid M. Metformin in patients with type 2 diabetes mellitus: reconsideration of traditional contraindications. *Eur J Intern Med.* 2002;13(7):428.

Cochrane Briefs

Usefulness of Measuring Antiepileptic Medication Blood Levels in Patients with Epilepsy

Clinical Question

Should persons with epilepsy have routine monitoring of medication blood levels to optimize treatment for preventing seizures?

Evidence-Based Answer

When treating a patient for epilepsy, there is not enough evidence to indicate if optimal seizure control is best obtained by routinely measuring medication levels compared with making adjustments based on the clinical picture. (Strength of Recommendation = C, based on consensus, disease-oriented evidence, usual practice, expert opinion, or case series)

Practice Pointers

Antiepileptic medications are the mainstay of epilepsy treatment. The goal is to maintain a medication dosage with as few seizures and adverse effects as possible. To achieve this, physicians often monitor drug levels in the blood. However, many have questioned if it is better to manage epilepsy by measuring therapeutic drug levels or by titrating medication dosages based on a patient's clinical picture.

In this Cochrane review, the authors did a meta-analysis that examined blinded and unblinded randomized controlled trials of antiepileptic drug monitoring. Participants were of all ages, had various seizure types, and were treated with any antiepileptic monotherapy. The intervention was measurement of antiepileptic drug concentration. Only two studies were identified, and only one prospective randomized study met the inclusion criteria of the review. The other study was excluded because patients were treated with more than one antiepileptic medication.

The study reviewed was an unblinded, prospective, parallel-group design of 180 patients with newly diagnosed, untreated epilepsy. Patients were randomized into a group with drug-level monitoring (intervention) or a group that used the clinical picture alone to alter medication dosage (control). The investigators found no difference in outcomes between the two groups. By 12 months, about 60 percent of patients from both groups achieved remission from seizures, and about one half reported adverse effects.

A position paper published in 2008 by the International League Against Epilepsy Commission on Therapeutic Strategies suggests that routine monitoring of therapeutic drug levels plays a valuable role in epilepsy treatment.[1] The paper's recommendations are based on nonrandomized studies and clinical experience, but it acknowledges that there have been no randomized controlled trials indicating the benefit of drug-level monitoring. Although routine monitoring remains the standard of care, it is important for physicians to know that it is not based on good-quality evidence and to watch for additional studies.

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REFERENCE

1. Patsalos PN, Berry DJ, Bourgeois BF, et al. Antiepileptic drugs—best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. *Epilepsia.* 2008;49(7):1239-1276. ■