

The Phantom of Lactic Acidosis due to Metformin in Patients With Diabetes

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Metformin is the only biguanide that is available in the U.S. Another biguanide, phenformin, had been used since the 1950s, but was declared an "imminent hazard" in 1976 because of lactic acidosis (1). At the time of its removal from the market, there had been 306 documented cases of phenformin-associated lactic acidosis (2), including 1 fatal and 2 nonfatal cases in the randomized controlled trial of the University Group Diabetes Program (3).

Metformin was marketed as Glucophage by Bristol-Myers Squibb in early 1995, with a boxed warning concerning the risk of lactic acidosis. Metformin had been used widely in Europe for several years, where it had been recognized that the risk of lactic acidosis from metformin was no greater than the risk of hypoglycemia from sulfonylureas (4).

Although the clinical utility of metformin had been recognized in the U.S. (5), its approval was undoubtedly delayed by the specter of phenformin and the lingering concern that metformin might also cause lactic acidosis. The eventual approval of metformin was unusually controversial. Crofford (6) predicted that metformin "will be widely used and will improve the outlook for many patients" with diabetes. But fear of lactic acidosis led the consumer advocacy group Public Citizen (7) to issue the warning: "Do not use Glucophage."

Based on data from Sweden, it was estimated that the risk of lactic acidosis in patients taking phenformin was ~10-fold

higher than the risk in patients taking metformin. A later report from Sweden (9) concluded that discontinuing metformin in aging patients when they developed renal or cardiovascular disease could further reduce the risk of lactic acidosis. The labeling of Glucophage reflected a belief that metformin had the potential to cause lactic acidosis, but that the risk could be mitigated by careful selection of patients.

To help allay concerns about the safety of metformin, Bristol-Myers Squibb committed to perform a large study (the Comparative Outcomes Study of Metformin Intervention Versus Conventional Approach [COSMIC]), comparing 1 year of treatment with metformin to "usual care" with other antidiabetic agents. The results of this study have recently become available (10). There were no meaningful differences in safety outcomes between the 7,227 patients who received metformin and the 1,505 patients who received usual care. There were no cases of lactic acidosis in either group.

Two large government-supported studies provide an impressive body of evidence to support the safety and effectiveness of metformin (11,12). In addition, several manufacturers other than Bristol-Myers Squibb have performed studies in which a new drug was used in combination with metformin or compared with metformin. Metformin is now indicated for use in combination with every other oral antidiabetic agent and insulin and is the only oral agent available in fixed-dose

combinations with other antidiabetic agents. Metformin is also specifically labeled for use in children with type 2 diabetes (13). In none of the studies submitted to the U.S. Food and Drug Administration (FDA) in support of these indications were there any episodes of lactic acidosis.

Salpeter et al. (14,15) reviewed published reports of controlled trials involving metformin that lasted 1 month or more and were reported through November 2002. They found no cases of lactic acidosis in 36,000 patient-years of exposure to metformin and concluded that there was no evidence to support a role for metformin in the development of lactic acidosis.

In contrast to the findings from controlled trials, cases of lactic acidosis continue to be reported in patients taking metformin. Among the first million patients (approximately) to have received metformin in the U.S., there were 47 reports (20 fatal) to the FDA of lactic acidosis. Of these patients, 43 had renal failure (labeled contraindication for metformin) or risk factors for lactic acidosis besides metformin (primarily congestive heart failure) (16). There were only four patients who did not have other risk factors for lactic acidosis when metformin was initially given. In one of these four case subjects, lactic acidosis appears to have been precipitated by an episode of urosepsis. None of these four patients died.

A recent review by Stades et al. (17) provides additional evidence that most cases of metformin-associated lactic acidosis, particularly fatal ones, are related to underlying conditions rather than to metformin. The authors went on to attribute many reports of metformin-associated lactic acidosis to a publication bias in which the widely held clinical impression that metformin causes lactic acidosis is erroneously fortified. I believe that this view is probably correct and cite as an example a report of "lactic acidosis" in a patient whose lactate level was only about 2 mmol/l (18 and see the technical note in the APPENDIX). On the other hand, there is a recent report by Dawson et al. (19) of

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Abbreviations: COSMIC, Comparative Outcomes Study of Metformin Intervention Versus Conventional Approach; FDA, Food and Drug Administration.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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severe lactic acidosis in a patient without risk factors other than metformin.

Lactic acidosis occurs in nondiabetic patients in association with infection, cancer, liver failure, and renal failure and is almost always a harbinger of death unless the underlying condition is corrected (20,21). In patients with type 2 diabetes, the rate of lactic acidosis is reported (22) to be similar in patients who are taking metformin and in patients who have never taken metformin. Mortality in patients with metformin-associated lactic acidosis appears to be ~40% and also appears to be associated with heart failure (16,17).

Stacpoole (23) has suggested that reports of metformin-associated lactic acidosis represent “guilt by association” with phenformin. Stades et al. (17) attributed many reports of metformin-associated lactic acidosis to the coincidence that diabetic patients are prone to develop serious medical conditions that lead to lactic acidosis. This view is shared by other authors (24) and is well taken. Patients with high blood levels of metformin appear less likely to die than patients with low levels of metformin, suggesting that lethality was related to the underlying cause (heart failure, hypoxia, etc.) rather than to metformin (17,25). Furthermore, the lack of correlation between lactate levels and metformin levels in these patients (25) strongly suggests that metformin is often an innocent bystander.

The number of documented cases of metformin-associated lactic acidosis is small when one considers how widely metformin is used (17). That metformin has been used safely in patients with contraindications (26–31) can be viewed as evidence that it does not cause lactic acidosis. On the other hand, cases of lactic acidosis from metformin overdoses (32), particularly in young people without risk factors (33,34), suggest that metformin can cause lactic acidosis if given in large doses.

Summary

Metformin rarely, if ever, causes lactic acidosis when it is used as labeled. Metformin is associated with lactic acidosis in patients with conditions that can themselves cause lactic acidosis (heart failure, hypoxia, sepsis, etc.). But it is impossible to determine to what extent, if any, metformin may contribute to the development of lactic acidosis in any individual

case. When metformin is used as labeled, the increased risk of lactic acidosis is either zero or so close to zero that it cannot be factored into ordinary clinical decision making. That metformin can itself cause lactic acidosis is supported by the finding of lactic acidosis in people who took overdoses. Thus, the accumulation of metformin in the setting of renal insufficiency might be expected to precipitate lactic acidosis in some patients who are at risk. If one excludes overdoses, most cases of metformin-associated lactic acidosis, particularly the fatal ones, were probably not caused by metformin.

APPENDIX

Technical note. Using venous blood obtained without a tourniquet after 2 h of rest, the upper limit of the 95% CI for plasma lactate was ~3 mmol/l for patients in COSMIC whether they were taking metformin or not (10). A similar finding was reported by DeFronzo et al. (35). Most authors have used a value of 5 mmol/l as the threshold for the diagnosis of lactic acidosis.

References

1. Meadows M: Why drugs get pulled off the market [article online], 2002. Available from http://www.fda.gov/fdac/features/2002/102_drug.html.
2. Misbin RI: Phenformin associated lactic acidosis: pathogenesis and treatment. *Ann Intern Med* 87:591–595, 1977
3. University Group Diabetes Program: A study of the effects of hypoglycemic agents on vascular complication in patients with adult-onset diabetes. V. Evaluation of phenformin therapy. *Diabetes* 24 (Suppl. 1):65–184, 1975
4. Campbell I: Metformin and the sulfonylureas: the comparative risk. *Horm Metab Res* 15 (Suppl.):105–111, 1985
5. Colwell JA: Is it time to introduce metformin in the United States? *Diabetes Care* 16:653–655, 1993
6. Crofford OB: Metformin (Editorial). *N Engl J Med* 333:588–589, 1995
7. Public Citizen: Do not use Glucophage (metformin). *Worst Pills, Best Pills* 1:5, 1995
8. Bergman U, Boman G, Wiholm BE: Epidemiology of adverse drug reactions to phenformin and metformin. *Br Med J* 2:464–466, 1978
9. Wiholm BE, Myred M: Metformin-associated lactic acidosis in Sweden 1977–1991. *Eur J Clin Pharmacol* 44:589–591, 1993
10. Cryer DR, Mills DJ, Henry DH, Nicholas

- SP: Comparative Outcomes Study of Metformin Intervention Versus Conventional Approach: the COSMIC approach study (Abstract). *Diabetes* 53 (Suppl. 1):A115, 2003
11. UK Prospective Diabetes Study Group: Effect of intensive blood glucose control with metformin on complications in overweight patients with type 2 diabetes (UK-PDS 34). *Lancet* 352:854–865, 1998
12. Diabetes Prevention Program Research Group: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393–403, 2002
13. Misbin RI: Placebo-controlled trials in type 2 diabetes (Commentary). *Diabetes Care* 24:773–774, 2001
14. Salpeter S, Greyber E, Pasternak G, Salpeter E: Risk of fatal and non-fatal lactic acidosis with metformin in type 2 diabetes. *Cochrane Database Syst Rev* 2: CD002967, 2003
15. Salpeter S, Greyber E, Pasternak G, Salpeter E: Risk of fatal and non-fatal lactic acidosis with metformin in type 2 diabetes. *Arch Intern Med* 163:2294–2602, 2003
16. Misbin RI, Green L, Stadel BV, Gueriguian JL, Gubbi A, Fleming GA: Lactic acidosis in patients with diabetes treated with metformin (Letter). *N Engl J Med* 338:265–266, 1998
17. Stades AME, Heikens JT, Erkelens DW, Holleman F, Hoekstra JBL: Metformin and lactic acidosis: cause or coincidence? A review of case reports. *J Int Med* 255: 179–187, 2004
18. Pepper GM, Schwartz M: Lactic acidosis associated with Glucophage use in a man with normal renal and hepatic function (Letter). *Diabetes Care* 20:232–233, 1997
19. Dawson D, Conlon C: Case study: metformin-associated lactic acidosis: could orlistat be relevant? (Letter). *Diabetes Care* 26:2471–2472, 2003
20. Stacpoole PW, Harman EM, Curry SH, Baumgartner TG, Misbin RI: Treatment of lactic acidosis with dichloroacetate. *N Engl J Med* 309:390–396, 1983
21. Lactic Acidosis Study Group: Natural history and course of acquired lactic acidosis in adults. *Am J Med* 97:47–54, 1994
22. Brown JB, Pedula K, Barzilay J, Herson MK, Latare P: Lactic acidosis rates in type 2 diabetes. *Diabetes Care* 21:1659–1663, 1998
23. Stacpoole PW: Metformin and lactic acidosis: guilt by association (Editorial). *Diabetes Care* 21:1587–1588, 1998
24. Jones GC, Macklin JP, Alexander WD: Contraindications to the use of metformin: evidence suggests that it is time to amend the list. *BMJ* 326:4–5, 2003
25. Lalau JD, Race JM: Lactic acidosis in metformin-treated patients: prognostic value

- of arterial lactate levels and plasma metformin concentration. *Drug Saf* 20:377–384, 1999
26. Sulkin TV, Bosman D, Krentz AJ: Contraindications to metformin therapy in patients with NIDDM. *Diabetes Care* 20: 925–928, 1997
 27. Emslie-Smith AM, Boyle DIR, Evans JMM, Sullivan F, Morris AD: Contraindications to metformin in patients with type 2 diabetes: a population-based study on adherence to prescribing guidelines. *Diabet Med* 18:483–488, 2001
 28. Horlen C, Malone R, Bryant B, Dennis B, Carey T, Pignone M, Rothman R: Frequency of inappropriate metformin prescriptions (Letter). *JAMA* 287:2504–2505, 2002
 29. Holstein I, Nahrwold D, Hinze S, Egberts EH: Contra-indications to metformin therapy largely disregarded. *Diabet Med* 16:692–696, 1999
 30. Rachmani R, Slavachevski I, Levy Z, Zadok B, Kedar Y, Ravid M: Metformin in patients with type 2 diabetes: reconsideration of traditional contraindications. *Eur J Intern Med* 13:428–433, 2002
 31. Masoudi FA, Wang Y, Inzucchi SE, Setaro JF, Havranek EP, Foody J, Krumholz HM: Metformin and thiazolidinedione use in Medicare patients with heart failure. *JAMA* 290:81–85, 2003
 32. Lalau JD, Mourlhon C, Bergeret A, La-Croix C: Consequences of metformin intoxication (Letter). *Diabetes Care* 21: 2036–2037, 1998
 33. Chang CT, Chen YC, Fang JT, Huang CC: Metformin-associated lactic acidosis: case reports and literature review. *J Nephrol* 15:398–402, 2002
 34. Medical officer's review of glucophage overdoses and lactic acidosis. Rockville, MD, Food and Drug Administration, 2004
 35. DeFronzo RA, Goodman AM: Efficacy of metformin in patients with non-insulin dependent diabetes mellitus. *N Engl J Med* 333:541–549, 1995