

Evaluation of Prescribing Practices

Risk of Lactic Acidosis With Metformin Therapy

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Background: The risk of lactic acidosis during metformin therapy is linked to specific and well-documented conditions that constitute contraindications or precautions to use of the agent. We conducted a retrospective evaluation of metformin use to determine whether prescribing practices are in accord with published contraindications and precautions.

Methods: All patients admitted to the hospital during a 6-month period who received at least 1 dose of metformin were identified through hospital pharmacy records. Patient demographics and clinical characteristics were then evaluated to determine whether metformin was prescribed to patients possessing any of the risk factors associated with development of lactic acidosis.

Results: We identified 263 hospitalizations involving 204 patients who received at least 1 dose of metformin during inpatient admission. Patients had at least 1 absolute

contraindication to metformin therapy in 71 admissions (27%). In 29 (41%) of these 71 admissions, treatment with metformin continued despite the contraindication. The most common contraindication, elevated serum creatinine concentration, was present or developed during 32 admissions (12%); however, metformin use was appropriately discontinued in only 8 (25%) of these 32 patients. Of the precautions against metformin use, concomitant administration of cationic agents was the most common, occurring in 97 admissions (37%).

Conclusions: Many patients are treated with metformin despite having clinical conditions that place them at risk for developing lactic acidosis. To minimize this risk, it is essential that prescribers develop a better understanding of the prescribing guidelines for metformin.

Arch Intern Med. 2002;162:434-437

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METFORMIN is a biguanide derivative that is used in the treatment of type 2 diabetes mellitus. It is currently considered the initial drug of choice for overweight patients (without contraindications) who have type 2 diabetes mellitus with or without dyslipidemia, and it is often used in sulfonylurea-treated patients who have not achieved their desired therapeutic goal.¹ Metformin is pharmacologically related to phenformin hydrochloride, which was withdrawn from the US market in 1976 (owing to an association with an unacceptably high incidence of lactic acidosis). Because of structural and pharmacokinetic differences between the compounds, the reported incidence of lactic acidosis with metformin therapy is 10 to 20 times less than that with phenformin use²; however, the literature contains numerous case reports of metformin-associated lactic acidosis. To reduce the likelihood of the development of lactic acidosis, the product labeling for met-

formin identifies the clinical conditions or patient characteristics that increase the risk of lactic acidosis.³ These precautionary conditions and contraindications are listed in **Table 1**.

Despite the availability of prescribing guidelines, metformin continues to be prescribed to patients at risk for lactic acidosis. For example, a 3-month review⁴ of prescribing patterns in a United Kingdom diabetes mellitus clinic concluded that more than half of the patients prescribed metformin had conditions that predisposed them to lactic acidosis. In another study⁵ from Europe, 73% of patients receiving metformin as outpatients had contraindications to its use on admission to the hospital.

We recently encountered a case of metformin-associated lactic acidosis at the University of Pittsburgh Medical Center Presbyterian (UPMC Presbyterian). Despite having severe ischemic cardiomyopathy and an ejection fraction of 15% (an absolute contraindication to the use of

MATERIALS AND METHODS

The Department of Pharmacy and Therapeutics at the UPMC *Presbyterian* provides operational pharmacy services to 42 nursing units using automation (unit-based dispensing cabinets and robotics) and satellite pharmacy services. Clinical pharmacists provide advanced pharmaceutical care in several patient care areas. The UPMC *Presbyterian* uses a 3-method system to identify adverse drug events: voluntary reporting, retrospective review of patients with E-codes (*International Classification of Diseases, Ninth Revision [ICD-9]*, code for adverse drug event), and computer surveillance.

This study was approved by the institutional review board of the University of Pittsburgh. All inpatients hospitalized at the UPMC *Presbyterian* between March 1, 1998, and August 30, 1998, who received at least 1 dose of metformin were identified through the hospital pharmacy database. Patient demographics and clinical characteristics were then evaluated to determine whether patients possessed any of the risk factors associated with lactic acidosis (Table 1). Comorbidities such as congestive heart failure (CHF) and chronic obstructive pulmonary disease were identified through ICD-9 codes. Laboratory records were reviewed to determine hepatic and renal function and pH values. Pharmacy and billing records were reviewed to determine whether patients received iodinated contrast dye or cationic drugs, including digoxin, procainamide hydrochloride, quinidine, and vancomycin. The χ^2 test and the Fisher exact test (depending on event frequency) were used to compare the frequency of specific risk factors in the admitting services.

metformin), the patient received the drug. This case raised our suspicion that failure to recognize factors that place patients at risk for lactic acidosis during metformin therapy may be more widespread than hitherto recognized. Therefore, we set out to determine the prevalence of risk factors for lactic acidosis in patients treated with metformin at the UPMC *Presbyterian*.

RESULTS

PATIENT POPULATION

During the 6-month study, there were 263 hospital admissions involving 204 patients to whom metformin was administered. The mean age of the group was 66 years (range, 34-93 years). The patient group was predominantly white (81%) and was equally divided among men (n=103) and women (n=101). Most admissions were to medical services, with the cardiology and general medicine services accounting for 109 admissions (41%). Of the 204 patients, 164 were admitted once, 28 were admitted twice, 7 were admitted 3 times, 4 were admitted 4 times, and 1 was admitted 6 times during the study. The median length of stay was 5 days (range, 1-80 days).

Table 1. Absolute Contraindications and Precautionary Conditions for Prescribing Metformin*

Absolute Contraindications	Precautionary Conditions
Renal disease or renal dysfunction (specifically, serum creatinine concentration ≥ 1.5 mg/mL [≥ 133 μ mol/L] in males and ≥ 1.4 mg/mL [≥ 124 μ mol/L] in females)	Age ≥ 80 y (unless measurement of creatinine clearance demonstrates that renal function is not reduced)
Congestive heart failure requiring pharmacological treatment	Clinical or laboratory evidence of hepatic disease
Acute or chronic metabolic acidosis	Concomitant cationic drug use
Metformin use should be discontinued at the time of a procedure requiring intravascular iodinated contrast material, for at least 48 h after the procedure, and until renal function is deemed normal	Presence of any condition associated with hypoxemia (eg, COPD and acute MI), dehydration, or sepsis
	Excessive alcohol intake
	After any surgery until patient's oral intake is resumed and renal function is deemed normal

*Data from the metformin package insert.³ COPD indicates chronic obstructive pulmonary disease; MI, myocardial infarction.

The discharge date was recorded as the day after the admission date in 43 (16%) of the 263 admissions.

RISK FACTORS FOR LACTIC ACIDOSIS

There was no statistical difference in the prevalence of contraindications ($P=.18$) or precautionary conditions ($P=.32$) in patients on the medical service vs a surgical service (Table 2). Table 3 gives the specific risk factors for lactic acidosis that patients had at the time of hospital admission or at some point during hospitalization. Of 204 patients receiving metformin, 126 (62%) had either an absolute contraindication to metformin use or a condition deemed to be a precaution. Sixty-four of these (31%) had at least 1 absolute contraindication to its use. Viewed from the standpoint of the total number of admissions, 159 (60%) of 263 involved patients with either an absolute contraindication or a precautionary condition, and 71 (27%) involved patients with 1 or more absolute contraindications. The most common absolute contraindication to metformin use in our population was an elevated serum creatinine concentration during hospitalization, occurring in 32 admissions (12%). No patients had an ICD-9 code for CHF. Of the precautions against metformin use, concomitant administration of cationic agents was the most common, occurring in 97 admissions (37%). In fact, the patient who was admitted to the hospital 6 times received vancomycin (a cationic drug that constitutes a precautionary condition) during 4 of those admissions.

We further evaluated whether metformin therapy was continued in patients possessing any specific risk factor for lactic acidosis. When all 71 admissions with at least 1 absolute contraindication were considered, 29 patients (41%) continued to receive metformin despite the contraindication. Table 4 gives the prevalence of metformin continuation by specific risk factor and by hospital service. Metformin use was continued in 24 (75%) of the 32 admissions during which an elevated serum cre-

Table 2. Prevalence of Absolute Contraindications and Precautionary Conditions by Hospital Service*

Service	Contraindications	Precautionary Conditions	Contraindications or Precautionary Conditions
Medical Services			
Cardiology	5/38 (13)	24/38 (63)	27/38 (71)
Family medicine	2/11 (18)	7/11 (64)	7/11 (64)
General medicine	17/71 (24)	32/71 (45)	42/71 (59)
Other†	17/49 (35)	16/49 (33)	27/49 (55)
Subtotal	41/169 (24)	79/169 (47)	103/169 (61)
Surgical Services			
Cardiothoracic surgery	13/25 (52)	21/25 (84)	21/25 (84)
General surgery	6/21 (29)	11/21 (52)	14/21 (67)
Neurosurgery	5/17 (29)	3/17 (18)	6/17 (35)
Other‡	6/31 (19)	15/31 (48)	15/31 (48)
Subtotal	30/94 (32)	50/94 (53)	56/94 (60)

*Data are given as number (percentage) of admissions.

†Includes dentistry, dermatology, endocrinology, gastroenterology, geriatric medicine, hematology/oncology, neurology, clinical pharmacology, pulmonary medicine, physical medicine, renal, and rheumatology.

‡Includes ophthalmology, orthopedic surgery, otorhinolaryngology, plastic surgery, transplantation, and urology.

Table 3. Summary of the Absolute Contraindications and Precautionary Conditions Identified in Patients Taking Metformin

Variable	Patients, No. (%) (n = 204)	Admissions, No. (%) (n = 263)
≥1 Contraindication	64 (31)	71 (27)
Elevated serum creatinine level	28 (14)	32 (12)
Congestive heart failure diagnosis	0	0
pH <7.35	19 (9)	19 (7)
Contrast dye	29 (14)	30 (11)
≥1 Precautionary condition	101 (50)	129 (49)
Age ≥80 y	21 (10)	27 (10)
Elevated aspartate aminotransferase or alanine aminotransferase	11 (5)	12 (5)
Concurrent cationic drug use	74 (36)	97 (37)
Chronic obstructive pulmonary disease	21 (10)	36 (14)
≥1 Contraindication or precautionary condition	126 (62)	159 (60)

atinine concentration was recorded. Similarly, 16 (53%) of 30 patients who received contrast dye during an admission received metformin the day after the contrast procedure. Of these 16 patients, a higher proportion were on the medical service compared with a surgical service ($P = .02$). There were no other statistical differences between the medical and surgical services in the observed frequency of metformin therapy continuation despite contraindications or precautions.

Nine patients who received metformin at some point during a hospital admission died. In 6 of these patients, the drug was given despite the presence of an absolute contraindication (elevated serum creatinine concentration in 4 patients and administration of contrast dye in 2 patients). In addition, 4 of these patients were older than 80 years, and 2 of them continued to receive met-

Table 4. Prevalence of Metformin Therapy Continuation Despite the Presence of an Absolute Contraindication or a Precautionary Condition*

Variable	Surgical Service	Medical Service	Total
Contraindications			
Elevated serum creatinine concentration	8/10 (80)	16/22 (73)	24/32 (75)
pH <7.35	0/4	3/15 (20)	3/19 (16)
Contrast dye†	2/10 (20)	14/20 (70)	16/30 (53)
Precautionary conditions			
Age ≥80 y	5/5 (100)	22/22 (100)	27/27 (100)
Elevated aspartate aminotransferase or alanine aminotransferase	2/6 (33)	3/6 (50)	5/12 (42)
Concurrent cationic drug use	39/39 (100)	58/58 (100)	97/97 (100)
Chronic obstructive pulmonary disease	16/16 (100)	20/20 (100)	36/36 (100)

*Data are given as number/total number (percentage).

† $P = .02$, surgery service vs medicine service.

formin despite a marked elevation in liver transaminase concentrations. In 2 patients who died and 1 who survived, elevated lactate concentrations were found (>7 mmol/L [63 mg/dL] in all patients, with a concentration as high as 11.9 mmol/L [107 mg/dL] in 1). In these patients, all of whom had renal dysfunction and 1 of whom had end-stage liver disease, there was a temporal relationship between metformin administration and the elevated lactate concentrations. Metformin-associated lactic acidosis (MALA) could not be ruled out in these 3 patients with the information available to us.

COMMENT

During the first year that metformin was available in the United States (actually May 1995 through June 30, 1996), 47 confirmed cases of lactic acidosis were reported to the Food and Drug Administration (FDA), which translates to an incidence rate of 5 per 100 000.⁶ Forty-three (91%) of the 47 cases occurred in patients at high risk for lactic acidosis because of preexisting cardiac disease, renal insufficiency, or chronic obstructive pulmonary disease with hypoxia. Twenty (43%) of these 47 patients died.

Although the reported incidence of MALA is rare, the product labeling for metformin states that the drug is contraindicated in patients with risk factors for lactic acidosis.³ Metformin increases intestinal lactate production and contributes to the hyperlactatemia seen in patients who accumulate metformin in the setting of a hypoxic event or defective lactate elimination (renal or hepatic failure).⁷ Despite this, it remains unclear whether metformin is a contributing cause of lactic acidosis or if it is merely a drug with a coincidental link to lactic acidosis. Nearly all reported cases of MALA occurred in patients who were already at high risk for lactic acidosis.^{7,8} However, it is impossible to refute with absolute confidence that such a relationship exists based on the currently available data. Reliance on incidence rates of MALA as reported to the FDA or equivalent governmental agen-

cies in other countries is confounded by the observation that the FDA may actually receive an official report of just 1% of all serious or fatal adverse drug reactions.⁹

The authors of a retrospective review of a large electronic health maintenance organization database determined that the overall rate of lactic acidosis in patients with type 2 diabetes mellitus before the availability of metformin (1993-1994) was similar to the incidence of MALA (as reported to the FDA in 1995-1996).⁸ A major limitation of this study, however, is that the approach used may underestimate the true magnitude of the association between metformin and lactic acidosis; the metformin-treated group may have been biased in favor of low-risk patients because of the known association of the drug with lactic acidosis, whereas the retrospective data set comprised "all-comers." In other words, the incidence of MALA might be higher if all individuals with diabetes mellitus are deemed eligible for the drug.

It remains important that physicians, nurse practitioners, physician assistants, and other health care professionals (including nurses and pharmacists) responsible for drug delivery remain aware of patient-specific factors that increase a patient's risk of MALA. Our analysis leads to the conclusion that metformin continues to be prescribed to patients who are at high risk for lactic acidosis. What is particularly alarming is the fact that the problem may be even more widespread than is evident from our data. The prevalence of risk factors in our study population was most likely underestimated for several reasons, most having to do with the retrospective nature of the study design. First, given patient age and concurrent medications taken, it is likely that CHF was a comorbidity for some, if not many, patients. Yet, none of the patients in the study were discharged from the hospital with an ICD-9 code for CHF. It is likely that CHF was not coded unless it was the medical problem that directly resulted in the current hospitalization. Second, data linking metformin use in patients with other relative contraindications, such as alcohol abuse, or patients receiving surgical procedures were not collected. Third, we were unable to ascertain whether patients discharged the same day as a procedure that required intravascular contrast material may have restarted metformin therapy before completion of the required 48-hour waiting period following dye administration. Thus, a limitation of this study is that the actual prevalence of risk factors may be significantly higher than that identified in this patient population.

It is also important to recognize that our study was designed neither to verify that metformin therapy causes lactic acidosis nor to suggest that metformin use should be avoided in all patients with relative precautions to the drug. Rather, we were interested in determining whether

prescribers were complying with the labeled contraindications and precautions to the use of metformin. In this regard, we determined that at the time of or some time during admission to the hospital, approximately 1 in 4 patients developed at least 1 absolute contraindication to the drug, and in nearly half of these, metformin therapy was continued despite the contraindication. This failure to recognize contraindications was just as likely to occur on a medical service (by those who may be "routine prescribers" of metformin) as it was on a surgical service (by those who may be less familiar with the drug).

Several relatively safe and effective drugs (terfenadine, astemizole, mibefradil dihydrochloride, bromfenac sodium, and cisapride) have recently been withdrawn from the US market mainly because they were used in patients with labeled contraindications.^{10,11} The US FDA has said that additional drugs will likely be removed from the market unless there is a change in the way health care professionals regard safety warnings.¹⁰ We believe that compliance with metformin prescribing guidelines is essential not only if MALA is to remain a rare entity but also if metformin is not to have a similar fate.

Accepted for publication June 6, 2001.

This work was presented in part as a poster at the American Diabetes Association 60th Scientific Sessions, San Antonio, Tex, June 12, 2000.

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REFERENCES

1. DeFronzo RA. Pharmacologic therapy for type 2 diabetes mellitus. *Ann Intern Med.* 1999;131:281-303.
2. Bailey CJ, Turner RC. Drug therapy: metformin. *N Engl J Med.* 1996;334:574-579.
3. Glucophage (metformin hydrochloride) [package insert]. Princeton, NJ: Bristol-Myers Squibb; December 1998.
4. Sulkin TV, Bosman D, Krentz AJ. Contraindications to metformin therapy in patients with NIDDM. *Diabetes Care.* 1997;20:925-928.
5. Holstein A, Nahrwold D, Hinze S, Egberts EH. Contraindications to metformin therapy are largely disregarded. *Diabet Med.* 1999;16:692-696.
6. Misbin RI, Green L, Stadel BV, et al. Lactic acidosis in patients with diabetes treated with metformin. *N Engl J Med.* 1998;338:265-266.
7. Lalau JD, Lacroix C, Compagnon P, et al. Role of metformin accumulation in metformin-associated lactic acidosis. *Diabetes Care.* 1995;18:779-784.
8. Brown JB, Pedula K, Barzilay J, Herson MK, Latare P. Lactic acidosis rates in type 2 diabetics. *Diabetes Care.* 1998;21:1659-1663.
9. Scott HD, Rosenbaum SE, Waters WJ, et al. Rhode Island physicians' recognition and reporting of adverse drug reactions. *R J Med J.* 1987;70:311-316.
10. Honig P, Phillips J, Woodcock J. How many deaths are due to medical errors? *JAMA.* 2000;284:2187-2188.
11. Woosley RL. Drug labeling revisions: guaranteed to fail? *JAMA.* 2000;284:3047-3049.