

## METFORMIN

Metformin is a biguanide oral anti-hyperglycemic agent used to treat patients with non-insulin-dependent diabetes mellitus. It is available as a generic drug as well as in proprietary formulations, alone and in combination with other drugs (see Table A for some of the brand name formulations). The drug was approved in the United States in December of 1994 for use as monotherapy or combination therapy in patients with non-insulin-dependent diabetes mellitus whose hyperglycemia is not controlled by diet or sulfonylurea therapy alone.

Metformin is thought to act by decreasing hepatic glucose production and enhancing peripheral glucose uptake as a result of increased sensitivity of peripheral tissues to insulin. Only rarely does it cause hypoglycemia.

The most significant adverse effect of metformin therapy is the potential for the development of metformin-associated lactic acidosis in the susceptible patient. This condition is estimated to occur at a rate of 0 to 0.084 cases per 1,000 patient years. Patient mortality in reported cases is about 50%. However, in almost all reported cases, lactic acidosis occurred because one or more patient-associated contraindications for the drug were overlooked. In one extensive 13 year retrospective study of patients in Sweden, 16 cases were found and all patients had several comorbid factors, most often cardiovascular or renal disease. There are no documented cases of metformin-associated lactic acidosis in properly selected patients.

Metformin is excreted unchanged by the kidneys, probably by both glomerular filtration and tubular excretion. The renal route eliminates approximately 90% of the absorbed drug within the first 24 hours. Metformin seems to cause increased lactic

acid production by the intestines. Any factors that decrease metformin excretion or increase blood lactate levels are important risk factors for lactic acidosis. Renal insufficiency, then, is a major consideration.

Also, factors that depress the ability to metabolize lactate, such as liver dysfunction or alcohol abuse, or increase lactate production by increasing anaerobic metabolism (e.g., cardiac failure, cardiac or peripheral muscle ischemia, or severe infection) are contraindications to the use of metformin (see Table B). Iodinated X-ray contrast media are not an independent risk factor for patients taking metformin but are a concern only in the presence of underlying renal dysfunction. Although contrast media-induced renal failure is very rare in patients with normal renal function, elderly patients with reduced muscle mass (and thus reduced ability to make creatinine) can have a “normal” serum creatinine level in the presence of a markedly depressed glomerular filtration rate.

Intravascular (IV) administration of iodinated contrast media to a patient taking metformin is a potential clinical concern. Of metformin associated lactic acidosis cases reported worldwide between 1968 and 1991, 7 of the 110 patients received iodinated contrast media before developing lactic acidosis. The metformin package inserts approved by the U.S. Food and Drug Administration states that metformin should be withheld temporarily for patients undergoing radiological studies using IV iodinated contrast media. If acute renal failure or a reduction in renal function were to be caused by the iodinated contrast media, an accumulation of metformin could occur, with resultant lactate accumulation. The major clinical concern, then, is confined to patients with known, borderline, or incipient renal dysfunction.

Limiting the amount of contrast medium administered and hydrating the patient lessen the risk of contrast media-induced dysfunction; both of these measures should be considered in patients with known or incipient renal dysfunction. The efficacy of other measures thought to limit contrast nephrotoxicity (e.g., administration of N-acetylcysteine) in preventing lactic acidosis related to metformin is not known (also see Chapter on Contrast Nephrotoxicity).

## Management

The management of patients taking metformin should be guided by the following:

1. Evidence suggesting clinically significant contrast-induced nephrotoxicity (CIN) induced by IV contrast injection is weak to nonexistent in patients with normal renal function [4].
2. Iodinated contrast is not an independent risk factor for patients taking metformin, but it is a concern in the presence of underlying conditions delaying renal excretion of metformin or decreased metabolism of lactic acid or increased anaerobic metabolism.
3. There have been no reports of lactic acidosis following IV contrast injection in properly selected patients.
4. In elderly patients, preliminary estimates of renal function relying on serum creatinine levels may be misleading and overestimate the adequacy of renal function.

The Committee recommends that patients taking metformin be classified into one of three categories, each of which has slightly different suggested management.

### *Category I*

In patients with normal renal function and no known comorbidities (see Table B), there is no need to discontinue metformin prior to intravenously administering iodinated contrast media, nor is there a need to check

creatinine following the test or procedure before instructing the patient to resume metformin after 48 hours.<sup>1</sup>

### *Category II*

In patients with multiple comorbidities (see Table B) who apparently have normal renal function, metformin should be discontinued at the time of an examination or procedure using IV iodinated contrast media and withheld for 48 hours. Communication between the radiologist, the health care practitioner, and the patient will be necessary to establish the procedure for reassessing renal function and restarting metformin after the contrast-enhanced examination. The exact method (e.g., serum creatinine measurement, clinical observation, hydration) will vary depending on the practice setting. A repeat serum creatinine measurement is not mandatory.<sup>1</sup> If the patient had normal renal function at baseline, was clinically stable, and had no intercurrent risk factors for renal damage (e.g., treatment with aminoglycosides, major surgery, heart failure, sepsis, repeat administration of large amounts of contrast media), metformin can be restarted without repeating the serum creatinine measurement.

### *Category III*

In patients taking metformin who are known to have renal dysfunction, metformin should be suspended at the time of contrast injection, and cautious follow-up of renal function should be performed until safe reinstatement of metformin can be assured.

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<sup>1</sup>The ACR Committee on Drugs and Contrast Media recognizes that the U.S. Food and Drug Administration (FDA) guidelines for metformin advise that for patients in whom an intravascular contrast study with iodinated materials is planned, metformin should be temporarily discontinued at the time of or before the study, and withheld for 48 hours after the procedure and reinstated only after renal function has been re-evaluated and found to be normal. However, the committee concurs with the prevailing weight of clinical evidence on this matter that deems such measures unnecessary.

## Metformin and Gadolinium

It is not necessary to discontinue metformin prior to gadolinium-enhanced MR studies when the amount of gadolinium administered is in the usual dose range of 0.1 to 0.3 mmol per kg of body weight.

**Table A**

### Medications containing Metformin\*

<u>Generic Ingredients</u>	<u>Trade names</u>
Metformin	Glucophage Glucophage XR Fortamet Glumetza Riomet
Glyburide/metformin	Glucovance
Glipizide/metformin	Metaglip
Pioglitazone/metformin	ActoPlus Met
Rosiglitazone/metformin	Avandamet

\*As of February, 2007. Additional medications containing metformin may have become available since then.

**Table B**

### Comorbidities for Lactic Acidosis with use of Metformin

Decreased Metabolism of Lactate
Liver dysfunction
Alcohol abuse
Increased Anaerobic Metabolism
Cardiac failure
Myocardial or peripheral muscle ischemia
Sepsis or severe infection

**Suggested Reading** (Articles that the Committee recommends for further reading on this topic are provided here.)

1. Bailey CJ. Biguanides and NIDDM. *Diabetes Care* 1992; 15:755-772.
2. Bailey CJ, Turner RC. Metformin. *N Engl J Med* 1996; 334:574-579.
3. Dunn CJ, Peters DH. Metformin. A review of its pharmacological properties and therapeutic use in non-insulin-dependent diabetes mellitus. *Drugs* 1995; 49:721-749.
4. Rao QA, Newhouse JH. Risk of nephropathy after intravenous administration of contrast material: a critical literature analysis. *Radiology* 2006; 239:392-397.
5. Schweiger MJ, Chambers CE, Davidson CJ, et al. Prevention of contrast induced nephropathy: recommendations for the high risk patient undergoing cardiovascular procedures. *Catheter Cardiovasc Interv* 2007; 69:135-140.
6. Sirtori CR, Pasik C. Re-evaluation of a biguanide, metformin: mechanism of action and tolerability. *Pharmacol Res* 1994; 30:187-228.
7. Thomsen HS, Almen T, Morcos SK. Gadolinium-containing contrast media for radiographic examinations: a position paper. *Eur Radiol* 2002; 12:2600-2605.
8. Wiholm BE, Myrhed M. Metformin-associated lactic acidosis in Sweden 1977-1991. *Eur J Clin Pharmacol* 1993; 44:589-591.