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Editorial

Guidelines for Performing Angiography in Patients Taking Metformin

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INTRODUCTION

Metformin (Glucophage) (Bristol-Myers Squibb, NY) is a biguanide antihyperglycemic agent recently introduced in the United States. Metformin-associated lactic acidosis has been reported to occur rarely, usually in diabetics with chronic renal insufficiency [1]. As a result of the potential for contrast-induced renal failure, metformin-treated patients who undergo angiographic procedures are theoretically at risk for metformin-associated lactic acidosis. This risk has created a problem for angiographers, as the use of metformin has increased.

Current guidelines for performing angiography in patients taking metformin are included in the manufacturer's recommendation that appears in the product brochure:

Parenteral contrast studies with iodinated materials can lead to acute renal failure and have been associated with lactic acidosis in patients receiving Glucophage. Therefore, in patients in whom any such study is planned, Glucophage should be withheld for at least 48 hours prior to, and 48 hours subsequent to, the procedure and reinstituted only after renal function has been re-evaluated and found to be normal [2].

This policy has the following limitations:

Difficulties may arise for patients who have not discontinued the drug before an angiographic procedure. These patients may suffer inconvenience, increased expense, and delayed medical care when the angiographic procedure is canceled.

The medical literature provides no evidence that withholding metformin for 48 hr before a contrast procedure in patients with *normal* renal function confers any protection.

No recommendations are provided regarding the management of patients who must undergo an urgent or emergency procedure while taking metformin.

Therefore, the members of the Laboratory Performance Standards Committee of the Society for Cardiac Angiography and Interventions explored the literature and propose the guidelines below for metformin-treated patients who require iodinated angiographic contrast material. These guidelines are not intended as a substitute for clinical judgment.

METFORMIN, RENAL FAILURE, AND CONTRAST MATERIAL

Metformin is excreted unchanged in the urine. Approximately 90% of the absorbed drug is eliminated via the kidneys within 24 hr. Metformin does not cause renal failure. In patients with renal failure, metformin may accumulate in body tissues and produce lactic acidosis.

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However, lactic acidosis that occurs during metformin therapy is not necessarily caused by metformin [3,4].

Lactic acidosis may be classified into anaerobic and aerobic types. Typically, lactic acidosis is anaerobic and is usually precipitated by cardiogenic or septic shock. It may occur as an unrelated event in metformin-treated patients. Metformin-associated lactic acidosis is aerobic and is associated with metformin accumulation in plasma, red blood cells, and tissue.

Metformin accumulation sufficient to produce lactic acidosis can occur only in the presence of renal failure (and rarely hepatic failure), and it occurs slowly [5–7]. In a patient with lactic acidosis, only increased metformin plasma and red blood cell (RBC) levels substantiate the causative role (or shared causative role) of metformin [6]. However, measurements of metformin levels are not available in most laboratories in the U.S. at this time.

The incidence of metformin-associated lactic acidosis is about 3 cases per 100,000 patient-years, and the mortality rate is about 1.5 cases per 100,000 patient-years [3–5]. No cases of metformin-associated lactic acidosis occurred during 56,000 patient-years over a 10-year period in Canada [4]. Since metformin became available in Europe in the late 1950s, there have been 13 published cases of metformin-associated lactic acidosis in patients with acute renal failure precipitated by iodinated contrast material. In 12 of the 13 cases, renal impairment existed before contrast administration, and in the remaining case, metformin therapy was continued after the onset of contrast-induced renal failure. In 10 of the 13 patients, metformin was continued after onset of contrast-induced renal failure. No cases of metformin-associated lactic acidosis have been documented in patients with normal renal function who discontinued metformin at the onset of contrast-induced renal failure.

REVISED GUIDELINES FOR IODINATED CONTRAST ADMINISTRATION IN METFORMIN-TREATED PATIENTS

A revised set of guidelines for administering iodinated contrast material to patients who are taking metformin is proposed below.

A. In elective cases, renal function should be evaluated before administering iodinated contrast material in all patients, including those taking metformin. Patients should be advised to discontinue metformin 2 days before the angiographic procedure. However, if a patient has taken metformin within 48 hr before a scheduled angiographic procedure, it is not necessary to cancel the procedure if the following policy is applied:

1. If renal function is normal,[1] iodinated contrast material may be administered without postponing the study. The patient should be adequately hydrated with intravenous fluids to minimize the likelihood of renal failure [8]. After the study, the patient may resume metformin after renal function is shown to be normal.
2. If renal function is abnormal, the contrast study should be postponed and the patient advised to contact the referring physician regarding discontinuation of metformin.

B. In emergency and urgent cases, serum creatinine level should be measured immediately and the following precautions taken:

1. If renal function is normal, the study may proceed as with elective patients.
2. If renal function is abnormal or unknown, the physician should weigh the risks and benefits of contrast administration and take the following precautions:

   Discontinue metformin.
   Correct hypovolemia; hydrate the patient during and after the procedure (saline 1 ml/kg/hR i.v., if hemodynamic status permits) [9].
   Correct low cardiac-output state, if possible.
   Administer a minimal volume of low-osmolality iodinated contrast material [10].
   Monitor urine output and renal function after the procedure.
   If acute renal failure occurs after contrast administration, observe the patient for symptoms and signs of lactic acidosis (e.g., abdominal pain, obtundation, hypotension, tachypnea). The diagnosis should be confirmed by arterial blood gas analysis and measurement of plasma lactate, glucose, and ketones (including beta-hydroxy butyrate).
   Consultation with a nephrologist and hemodialysis should be considered if lactic acidosis occurs [11].

[1]The upper normal level of creatinine varies among laboratories and in relation to muscle mass.

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