Commentary

Intravenous iodinated contrast media and metformin: interactions and precautions

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According to the last National Survey of Risk Factors conducted in Argentina (2009), the prevalence of diabetes is 11.9% [(1)] About 90% of diabetic subjects have diabetes type 2 and this figure grows every year as a result of a poor diet, overweight, obesity and an increased life expectancy.

As most of these patients die from atherosclerosis or ischemic heart disease or suffer from kidney disease, they are expected to require a large number of diagnostic tests with intravenous (IV) iodinated contrast media (angiography, urography, chole-cystography, computed tomography, etc.).

Metformin is a first-line oral antidiabetic drug, therefore it is commonly used by patients with type 2 diabetes undergoing contrast-enhanced tests.

The medical literature reports several cases of lactic acidosis, a serious adverse effect in patients treated with metformin who undergo studies involving IV iodinated contrast media.

This paper focuses on the interactions and precautions in diabetic patients receiving metformin who must undergo a study with IV iodinated contrast media.

Patients with diabetes and renal function

Diabetes is the most common cause of chronic renal failure and the main cause of end-stage renal disease. Forty percent of adults with diabetes and 17.7% of adults with prediabetes have some renal function impairment [(2)].

Based on these statistics, diabetic patients commonly have some degree of renal failure. As creatinine clearance (considered as the gold standard for assessing renal function) is not available for all patients before the study, it may be predicted from serum creatinine, theoretical weight and age of the patient using the Cockroft-Gault formula:

CrCl (males) in ml / min = (140 - age) x IBW / (72 x Scr)

CrCl (females) in ml / min = (140 – age) x IBW x 0.85 / (72 x Scr)

[Scr = serum creatinine (mg / dL), CrCl = creatinine clearance, IBW = ideal body weight]

The Sociedad Española de Nefrología (Spanish Society of Nephrology) has a useful online calculator that provides an immediate calculation from the data entered (age, gender, serum creatinine, weight and height) [(3)].

Pharmacological features of metformin

Metformin is the main oral antidiabetic drug that lowers blood glucose levels without causing hypoglycemia or weight gain.

This drug has multiple and extrapancreatic actions:

- It inhibits glucose formation
- It decreases intestinal glucose absorption
- It promotes the uptake of glucose in muscle, adipose tissue, and other tissues, as it increases the expression of glucose transporter GLUT4.

Metformin is absorbed at intestinal level by approximately 60%, it is negligibly bound to plasma proteins and is eliminated unchanged by glomerular filtration and tubular secretion (no metabolites or enterohepatic circulation have been identified). Following administration, 90% of the absorbed drug is eliminated within the first 24 hours. It has a half-life of approximately 6.2 hours (ranging from 4 to 9.2 h) [(4)].

Lactic acidosis is the most dangerous adverse effect of metformin (this is the reason why another drug of the same class has been withdrawn from the market). This condition is associated with a mortality rate of 40% and risk factors that contraindicate the administration of metformin have been identified to prevent its occurrence, namely:

- Chronic hypoxemic conditions
- Respiratory failure
- Hepatic failure
- Heart failure
- Renal failure
- Sepsis or severe infection

These factors depress the ability to metabolize lactate (as it is the case of hepatic failure or alcohol abuse) or increase lactate production (in the case of heart failure, respiratory failure, peripheral muscle ischemia or severe infection).

The initial symptoms of lactic acidosis are insidious:

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Recibido: abril 2011; aceptado: agosto 2011
Received: april 2011; accepted: august 2011

general poor health, hyper-ventilation, hypotension, vomiting, abdominal pain and stupor. The diagnosis is confirmed by increased blood lactate concentration and acidosis.
The mechanism of lactic acidosis induction by metformin is complex and it is associated to the shift of glucose metabolism from aerobic to anaerobic, resulting in an increased production of lactate by the cells. Lactic acidosis results from an increase in blood levels of metformin due to a decrease in its clearance because of renal failure [5].
Even if metformin does not cause renal failure as an adverse effect, it is counter indicated in patients with renal impairment because of the possibility of leading to fatal lactic acidosis.

Pharmacological characteristics of iodinated contrast media

Iodinated contrast media, when administered intravenously, have a distribution volume of approximately 0.28 l/kg of body weight, a value consistent with distribution in the extracellular space. These media have very low binding to proteins (<10%) and their half-life is short (2-3 hours). They do not undergo hepatic metabolism and are excreted unchanged via the renal route, almost entirely by glomerular filtration.
In patients with normal renal function, over 90% of contrast media is eliminated within the first 24 hours. In some patients, especially in the elderly and children, glomerular filtration may be decreased by up to 50%, even with normal serum creatinine levels (for example, due to reduced muscle mass). This could result in an increase in the half-life of iodinated contrast media and metformin, which would stay in the body for a more prolonged time.

Coadministration of iodinated contrast media and metformin

There are several published cases of death from lactic acidosis in patients who were taking metformin and underwent studies involving the administration of IV iodinated contrast media [6, 7, 8, 9].
Evidence of lactic acidosis in patients receiving metformin undergoing studies with iodinated contrast media is based on a isolated case reports that have been heterogeneously studied.
IV iodinated contrast media are not an independent risk factor from lactic acidosis in patients taking metformin, but they are a concern in the presence of underlying renal disorders. Although contrast media-induced renal failure is very rare in patients with normal renal function, elderly patients with reduced muscle mass may exhibit a normal serum creatinine level in the presence of a markedly depressed glomerular filtration rate.
The Food and Drug Administration (FDA) established that prescription information should state that metformin should be temporarily withheld for patients undergoing studies using IV iodinated contrast media, as they may cause acute renal failure and promote the accumulation of metformin and lactic acidosis [2, 10, 11, 12].
Almost all the Diagnostic Imaging Societies have guidelines for the use of IV iodinated contrast media in patients receiving metformin. With slight variations, these guidelines in general recommend that metfor-

Table 1: Risk categories for the administration of IV iodinated contrast media in patients receiving metformin.

Category I	With normal renal function and no comorbidities.	There is no need to discontinue metformin, nor is there a need to check serum creatinine levels.
Category II	With normal renal function, but with comorbidities for lactic acidosis, such as: - Decreased metabolism of lactate - Increased anaerobic metabolism - Liver dysfunction - Alcohol abuse - Cardiac or respiratory failure, sepsis, severe infection, etc. or - Concomitant administration of nephrotoxic medications (including, but not limited to, aminoglycosides). or - Repeated use or high doses of IV contrast media.	Metformin should be discontinued at the time of the study and withheld for 48 hours. Reinstitution of metformin will depend on the patient's clinical observation. Communication between the radiologists and the healthcare practitioners is important in this category for restarting metformin.
Category III	With abnormal renal function.	Metformin will be discontinued at the time of the study and cautious follow-up of renal function should be performed for reinstitution of metformin.

Source: Manual on Contrast Media (version 7), American College of Radiology, 2010.

min should be withheld 48 hours before the study in patients with creatinine clearance below 30 mg/dL or serum creatinine levels > 1.5 mg/dL [13, 14, 15].

The American College of Radiology (ACR), in its 7th edition, 2010 [16] divides patients into different risk categories (according to the creatinine clearance and the presence of comorbidities) and recommends temporary discontinuation periods for metformin (Table 1).

There have been no reports of lactic acidosis in patients undergoing studies involving IV iodinated contrast media when patient screening guidelines were followed [13]. In elderly patients it is important to know if their renal function is adequate.

Practical conclusions

1. It should be born in mind that renal function, which is critical for the elimination of IV iodinated contrast media and metformin, is commonly impaired in diabetic patients.
2. Remember that an increase in plasma metformin may result in a serious life-threatening condition: lactic acidosis.
3. Patients taking metformin should be identified by specifically asking: "Are you diabetic?" and if the answer if yes: "Are you taking metformin?"
4. Renal function (actual creatinine clearance or estimated by formula) and the presence or absence of comorbidities for lactic acidosis should be known.
5. Proceed according to the risk categorization of the American College of Radiology.

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The authors declare no conflicts of interest.