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Intravenous contrast agents in diabetic patients taking metformin; an updated review on current concepts

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ABSTRACT

Iodinated contrast agents are routinely used to diagnose a variety of diseases especially malignant tumors. They are crucial for accurate depiction of tumors, monitoring the response to treatment, and assessing possible recurrence of malignant lesions. Unfortunately, there are potential adverse effects associated with their administration. Metformin as an antidiabetic drug is prescribed widely. The drug is usually administered to control type II diabetes mellitus. One of the most important side effects of metformin is the possibility of lactate accumulation and occurrence of metformin-associated lactic acidosis (MALA), which develops under various circumstances including decreased renal function or concurrent use of toxic agents. Since, intravascular injection of iodinated contrast agents for radiologic purposes may result in kidney injury, it is suggested that metformin should be held in diabetic patients with renal failure before administration of contrast media and not to be taken by the patient again till 48 hours after the procedure and assessment of kidney function which should be normal.

Review

Implication for health policy/practice/research/medical education:
Diabetic individuals with renal failure using metformin are at high risk of metformin-associated lactic acidosis if they are scheduled for iodinated contrast study.

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Introduction

Diabetes mellitus is the main cause of chronic kidney disease and end-stage kidney failure. Metformin is a commonly prescribed oral antidiabetic agent. It is usually administered by individuals with diabetes type II. It is a biguanide administered mainly as an oral hypoglycemic substance in the therapy of this disease (1). Metformin has several pancreatic actions. It prevents glucose creation, raises the uptake of glucose in muscles, adipose tissues and reduces intestinal glucose absorption, while this drug also enhances the glucose transporter GLUT4 expression (2). Metformin boosts the cells response to insulin and diminishes liver gluconeogenesis and has renal excretion.

It is also administered in the treatment of non-alcoholic fatty liver disease and polycystic ovary syndrome. One of the most important side effects of metformin treatment is the possibility of lactate accumulation and an increased incidence of metformin-associated lactic acidosis (MALA). MALA might develop under various circumstances including decreased lactate metabolism similar to alcohol abuse or hepatic dysfunction, concurrent use of nephrotoxic drugs, enhanced anaerobic metabolism similar to renal failure and severe infection or cardiac impairment (3). It is believed that lactic acidosis as an acute adverse effect of this drug can occur when individuals are exposed to intravenous iodinated contrast medium (4,5).

Since, some reports of mortality due to lactic acidosis came from individuals who were taking this drug, therefore in this review we are considering hazards of contrast

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medium injection in individuals who take metformin.

Since most of diabetic patients develop atherosclerosis, diabetic kidney disease and ischemic heart disease, thus they are anticipated to need various diagnostic tests with intravenous iodinated contrast agents. Contrast medium, as injection or orally helps to provide clear radiographic images, like computed tomography (CT) scans, intravenous urogram, angiographic studies including coronary catheterization and cholangiography. The contrast mediums have relatively short half-life of about two to three hours. Contrast agents, directly excrete through kidney system mostly from glomerular filtration, since they are not metabolized by the hepatobiliary system. In individuals with appropriate kidney function, more than ninety percent of contrast agent is removed during the first 24 hours. In various circumstances, particularly in old population, the filtration of glomeruli (GFR) could be reduced as low as 50% of normal values even in the presence the presence of normal plasma creatinine levels. This condition will result in increased half-life of both iodinated contrast agents and metformin. In this situation metformin might remain in the circulation more than usual (6).

Diabetic individuals on metformin who need intravenous contrast agents may suffer from renal disease too. As a result, they are predisposed to develop MALA more than the general population especially after receiving intravenous iodinated contrast medium (7). It has been observed that intravenous injection of iodinated contrast agents for radiographic purposes has been related to a decrease in kidney function, a condition named contrast associated acute kidney injury which may accelerate lactic acidosis in diabetic patients who receive metformin, because presence of renal insufficiency is another considerable risk factor of developing MALA in such patients (8). However, no recognized interaction has been reported between iodinated contrast medium and metformin in renal failure (9).

Methods and Materials

For this review paper, we used several sources including Google Scholar, Web of Science, PubMed, Embase, Scopus and directory of open access journals (DOAJ) and others. The search was conducted using combinations of the following keywords or their equivalents; metformin, contrast medium, diabetes mellitus, metformin-associated lactic acidosis, renal injury, diabetic kidney disease, chronic kidney disease, end-stage kidney failure and contrast-induced nephropathy.

Metformin pharmacokinetics

Metformin is easily absorbed through small intestine and reaches the peak level after 2.5 hours of ingestion. Kidney excretion of this drug is fast since 90% of the drug is excreted through tubular secretion and glomerular filtration in the first twelve hours. In addition, in sustain released forms of metformin, a polymer layer surrounds the metformin and retards its absorption. Therefore, the peak blood concentration is achieved as late as seven hours after ingestion however, the clearance is the same as fast release type of this drug (10).

Metformin therapy and the risk of lactic acidosis

Lactic acidosis is a medical condition caused by excess production of lactate in the body. In fact, lactic acidosis is usually the outcome of an underlying acute or chronic medical disorder, drugs or poisoning. Generally, the signs are attributable to the underlying reasons, however vomiting, nausea, Kussmaul breathing, and generalized frailty are common (11). Notably, the initial warning signs of lactic acidosis are insidious. Other findings are abdominal pain, stupor, hypotension and hyperventilation. The diagnosis of lactic acidosis is established by elevated plasma lactate levels and presence of high anion gap metabolic acidosis. It is possible that renal dysfunction owing to iodinated contrast medium, increases the blood level of metformin and consequently increases the risk of lactic acidosis.

The pathophysiology of MALA is multifaceted, since it is caused by the alteration of glucose metabolism commonly from aerobic to anaerobic metabolism, ensuing in a strengthened creation of lactate substance by the cells. Lactic acidosis also results from an escalation in plasma concentration of metformin caused by reduction of the renal excretion of the drug due to renal insufficiency (6).

Therefore, guidelines advise to stop taking metformin in the period of receiving intravenous contrast agents, and withheld it for at least two days after the procedure, and re-commenced only when kidney function is normal (11).

Accordingly, the chance of lactic acidosis with the other biguanide, phenformin, was found to be undesirable while, it was removed in the late 1970s. In fact, the chance of developing lactic acidosis with phenformin was observed to be much more than metformin (10). More recent studies concluded that the chance of MALA in diabetic patients ranges from 4.3 to 9 cases per 100 000 person-year (11), however the chance of developing metformin- related lactic acidosis is not more than that of sulphonylurea (12).

Iodine-based contrast media

Individuals with diabetes and impaired kidney function are at increased risk of contrast medium-induced nephropathy compared with non-diabetic patients with similar degree of kidney function. it is possible that the condition of the diabetic patients with kidney disease gets complicated by contrast medium nephropathy after receiving intravascular iodine–based contrast media,

since there is a chance for metformin retention and lactic acidosis in these patients. These potential risks have imposed limitations on the use of metformin when there is a need for iodine–based contrast medium usage (12). In fact, there is a shortage of data when it comes to the instructions regarding administration of iodine–based contrast media in the patients taking metformin, while older instructions recommended that metformin should be discontinued two days before iodine-based contrast media injection and not be taken again until two days after the study in patients with normal renal function (13).

Non-ionic contrast agent

The kind of administered contrast agent is a key risk factor for the development of contrast medium-induced nephropathy, low-osmolar and iso-osmolar contrast agents are less nephrotoxic than high-osmolar contrast mediums in individuals with pre-existing kidney injury (8). As a result, iso-osmolar or low-osmolar non-ionic contrast agents are suggested in high-risk patients to decrease the chance of contrast medium-induced nephropathy. However, there is no difference in nephrotoxicity between non-ionic monomers and non-ionic dimers, since a total of eight non-ionic monomeric low-osmolar contrast agent, one ionic dimeric low-osmolar contrast agent, and one non-ionic dimeric iso-osmolar contrast agent are approved for intravascular injection (8,14).

Discussion

Metformin is an oral antihyperglycemic drug extensively administered for therapy of type 2 diabetes mellitus. The drug is removed unchanged by the kidneys (more than 90% during 24 hours). This drug also is a biguanide, which accelerates the production of lactic acid too. If the injection of radio-contrast material initiates kidney injury, metformin is not excreted consequently and can attain the toxic concentration leading to lactic acidosis which is accompanying by significant mortality (~50%). Hence, it is advocated that metformin be stopped at least twelve hours prior to the contrast material injection and be held for a minimum of 36 hours after the radiographic imaging, or even lengthier if the plasma creatinine has not reached to its baseline (11).

The present guidelines state that metformin should not be administered when the serum creatinine of patients is more than 1.5 mg/dL in males or more than 1.40 mg/dL in females (15-18).

Other guidelines on the administration of contrast medium in patients receiving metformin recommend the above (19, 20).

Plasma creatinine value would be assessed in each diabetic individual on biguanides before intravascular injection of contrast agent.

In diabetic patients, low and iso osmolar contrast media is preferred over the other types of contrast agents.

Elective procedures

- If renal function is normal, the radiological procedure would be conducted but the metformin should be ceased from the time of the procedure. The administration of metformin must not be re-started for 48 hours and can be restarted only if kidney function returns toward baseline range.
- If serum creatinine is raised, the drug would be discontinued and the contrast media injection would be postponed for forty-eight hours, then metformin would be re-continued forty-eight hours later, if kidney function is preserved (21-25).

Emergent conditions

The procedure could be conducted if kidney function is normal, as proposed for elective individuals.

- In the condition of renal failure, we would assess the risks and benefits of contrast agent injection, while alternative procedures may also be considered.
- If contrast agent injection seems necessary, first metformin administration should be discontinued, then hydration of patient should be envisaged (26-29).

Intravenous contrast mediums are known to increase the risk of acute renal insufficiency too (30, 31). Nonetheless, it is still controversial, if high metformin blood level itself can be the lone parameter accountable for MALA. The only evidence which indicates that the use of metformin is associated with lactic acidosis comes from reports of ~330 cases that have occurred in patients while on metformin treatment (32). Although there is not strong academic evidence supporting that metformin is lonely responsible for lactic acidosis, current recommendations are in favor of stopping metformin administration and retest the kidney function after intravascular contrast medium administration, though the recommendations vary among professional international radiological organizations (33-36).

Most cases of lactic acidosis occur in patients with abnormal renal function, while lactic acidosis seems to be rare in patients with normal baseline renal function before contrast medium administration.

Conclusion

It seems that a controversy exists between clinicians regarding discontinuation of metformin in the setting of iodinated contrast medium administration. Taking all of the above discussions into consideration, the following recommendations appears to be a logical approach.

As the intravascular injection of iodinated contrast

agents for radiologic purposes may direct toward kidney injury, metformin in diabetic patients who had renal impairment should be withdrawn prior to, or at the period of radiologic procedure and not to be restarted till 48 hours subsequently, the drug can be re-administered only if kidney function has been reevaluated and detected to be normal (14,19).

In brief, lactic acidosis is developed by an accumulation of lactic acid in the blood. Even though rare, however, lactic acidosis can be life threatening, that is why the other drug of the biguanide family was removed from the market place. This circumstance is related to a death rate of forty percent. To avoid the occurrence of this adverse effect, conditions that reduce the capability of lactate metabolism such as chronic hypoxemic state, heart failure, hepatic insufficiency, renal injury, respiratory diseases, sepsis and serious infections should be identified and treated.

Authors' contribution

MA and RD searched the data and prepared the draft of the manuscript. SE edited the paper. SHM edited and finalized the paper. All authors read and signed the final manuscript.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication and double publication) have been completely observed by the authors.

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