Metformin Associated Lactic Acidosis and Iodinated Contrast Media

Definition
Metformin associated lactic acidosis is referred to the development of lactic acidosis due to the use of metformin in patients with type II diabetes mellitus. Usage of metformin in NIDDM patients does not cause MALA. However, if these patients have concomitant illness such as acute cardiorespiratory dysfunction, sepsis, renal dysfunction, or liver failure, these will increase the risk of developing MALA.

Epidemiology
Metformin associated lactic acidosis (MALA) is rare but once it has developed, it could result in severe consequences. Research was conducted in Saskatchewan, Canada, on the incidence of MALA. Data between 1980 and 1995 was collected and analyzed. The results indicated the incidence of MALA is approximate 9 cases per 100,000 person-years (adding number of days of each prescription) for patients taking metformin.

Pathophysiology
Metformin associated lactic acidosis can occur in patients with normal renal function. It can also result after diagnostic examinations or procedures with parenteral injection of radiographic iodinated contrast media.

Metformin
The two major groups of oral hypoglycemic agents are sulphonylureas such as glyburide and biguanides such as metformin and buformin. Metformin is the first line oral antihyperglycemic agent for patients with non-insulin dependent diabetes mellitus (NIDDM or type II DM). It is called an antihyperglycemic agent as it does not stimulate the production of insulin and will not cause hypoglycemia. Metformin is hydrophilic and not bound with plasma protein; it is mainly absorbed in the small intestine. Metformin is not metabolized in the body and is excreted unchanged via the renal system.

Actions of metformin include decreasing gluconeogenesis in liver, decreasing intestinal glucose absorption, increasing insulin sensitivity, promoting peripheral cellular glucose uptake, and increasing glucose oxidation. Plasma half-life of metformin is about 2-5 hours for patients with normal renal function. Metformin blocks the conversion of lactate in liver, which can result in lactate accumulation.

Metformin associated lactic acidosis could be the combined result of increased anaerobic metabolism of glucose (increased production of lactate) in the intestinal wall and decreased conversion of lactate into glucose in the liver.

Contrast Medium Nephrotoxicity
Contrast medium nephrotoxicity (CMN) is defined as an acute decline in renal function after administration of ICM. Reduction in renal function usually occurs within 72 hours post ICM injection. Iodinated contrast media has demonstrated several mechanisms that cause renal tubular epithelial cell toxicity and renal medullary ischemia that result in decreasing renal function. ICM stimulates the release of endogenous vasoconstrictors such as endothelin and adenosine and reduces the release of vasodilators such as nitric oxide and prostacyclin. The imbalance of vasoconstrictors and vasodilators causes decreases in renal blood flow, which leads to a decrease in renal function. ICM also activates the oxygen free radicals and damages the renal tubules. Most CMN are self-limiting and resolve within 1 - 2 weeks, however, permanent renal damages have also been documented.

Metformin associated Lactic Acidosis Resulted from the use of Iodinated Contrast Media
Metformin is not nephrotoxic and does not interact with iodinate contrast media. However, if CMN occurs, metformin excretion will be decreased. Excessive accumulation of metformin may result in metformin associated lactate acidosis. The risk of MALA is very low (0.005%), however, mortality rate of patient with MALA is about 50%.

Prevention measures of MALA post ICM injection include intravascular volume expansion. Some researchers suggest intravenous infusion of NaCl 0.9% 100mL/h starting 4 hours before the procedure with ICM and continuing with the infusion for 24 hours post procedure if not contraindicated. Avoid concomitant uses of nephrotoxic medications. Acetylcysteine is an antioxidant that inhibits production of hydrogen peroxide in renal epithelial cells. Use of acetylcysteine as prophylaxis for patient with decreased renal function is also suggested.
Diagnostic test

Metformin associated lactic acidosis is a high anion gap metabolic acidosis. Arterial blood gas results with pH < 7.35 and serum lactate > 5.0mmol/L with no other causes can be diagnosed as MALA.

Treatment Options

The goals of treatments for MALA include earlier recognition of the problem, supportive care, correct acid-base imbalance, volume expansion, and elimination of metformin by hemodialysis or continuous hemofiltration. Using bicarbonate to correct acidosis should be used with caution because of its side effects such as excessive sodium load, and rebound metabolic alkalosis.

Hemodialysis or continuous hemofiltration has demonstrated good effects in metformin and lactic acid clearance.

Nursing Implication

It is important to assess the patients’ renal function before any diagnostic tests that involve injection of ICM. If the patient’s renal function is compromised, the physician should be notified before the procedure. Many health care institutions have developed policies for pre-diagnostic test screening, which include assessing the patient’s renal function.

Monitor for any signs of lactic acidosis such as tachycardia, hypotension, stupor, and coma post procedure.

Monitor for any signs of allergic reaction from the ICM such as flushing, nausea and vomiting, pruritus, headache, and urticaria. In severe cases, patients may develop hypotension and bronchospasm.

Several researchers and guidelines have suggested metformin should be held 48 hours before and 48 hours after a patient’s angiogram or any tests required ICM. However, in emergency situations, if the diagnostic test with ICM is required, metformin should be held 48 hours after the test. The patient should receive alternate medication such as insulin to control their blood sugar during the time metformin is on hold. If renal function is normal at 48 hours, metformin can be restarted.

Currently, there is no consensus from the international guidelines about withholding metformin before and/or after the administration of ICM. However, diabetes patients who take metformin can develop MALA even if they have normal renal function post administration of ICM. Individual institutions should develop their own policy and guideline carefully to avoid the occurrence of CMN induced MALA.

Reference


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Diagram Showing the Interaction of Iodinated Contrast Medium and Metformin