ISSN: 2278-2648

International Journal of Research in Pharmacology & Pharmacotherapeutics (IJRPP)

IJRPP |Vol.13 | Issue 1 | Jan - Mar -2024

www.ijrpp.com

DOI : https://doi.org/10.61096/ijrpp.v13.iss1.2024.24-30

Case Study

Metformin Associated Lactic Acidosis: A Rare Life Threatening Complication

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Published on: 14 Feb 2024

Published by:
DrSriram Publications

Abstract

Metformin-Associated Lactic Acidosis (MALA), a potential complication of metformin therapy in type 2 diabetes patients. It highlights the medication's role in managing blood glucose, its influence on renal function, and the associated risk factors, including age and comorbidities. The pathophysiology of MALA is explored, emphasizing how metformin affects mitochondrial function and leads to lactate accumulation and acidosis. A clinical case presentation underscores the real-world implications of this condition. The article concludes by stressing the importance of early recognition and discontinuation of metformin, ultimately encouraging healthcare providers to consider individualized patient risk factors when prescribing metformin.

Keywords: diabetes, dialysis, drugs, MALA.

I. INTRODUCTION

Metformin is categorized under the class of biguanides of anti diabetic drugs. This helps to control the levels of blood glucose amongst people suffering from diabetes. Biguanides includes phenformin, buformin and metformin. Metformin is used as an anti diabetic drug in obese / overweight patients who have type 2 DM. Apart from being an anti diabetic drug /anti hyperglycemic medication, metformin is also responsible for reducing the risk of cardiovascular diseases in patients with diabetes who are overweight/obese. Biguanides are responsible to lower the blood glucose levels by producing insulin like effects on tissues, however these biguanides do not cause hypoglycemia ,moreover are responsible to cause weight reduction (due to anorexia). Biguanides when used as 'off label' may have the chances to cause obesity, hirsutism and infertility in patients who are having PCOD's. Biguanides may contribute to nephro, liver and cardiac diseases[1-2].

Biguanides are known to suppress the gluconeogenesis in hepatic cells by activation of Amp Activated Protein Kinase(AMPK) which is responsible for the controlled cellular metabolism of lipids. Biguanides are also

known to inhibit the intestinal absorption of glucose and also to stimulate the process of glycolysis in the body tissues. Moreover, the biguanides are responsible to stimulate the peripheral uptake of glucose in presence of insulin in tissues and to decrease the levels of glucagon in plasma in addition to reducing the appetite. The phenformin was discontinued due to the high risk of lactic acidosis. The phenformin was banned by the FDA as it caused more cases of phenformin associated lactic acidosis. It was banned as it caused a huge amount of cases i.e about 40-64 cases per 100,000 cases per 3 to 6 years and also had a 50% fatality rate. However, metformin is safer than phenformin as it has less no of cases of MALA when compared to the phenformin i.e 0-8.4 cases per 100,000 cases per 4-6 years. According to the American association of poison control centers, have stated that metformin may have contributed to 21 fatalities in USA in 2008[3-5].

Metformin, (1, 1 - dimethyl biguanide) is a small molecule of about 165 KDa,is widely used in the treatment of non insulin dependent diabetes mellitus. It is absorbed by the stomach and is well absorbed. It has about 50% of bioavailability and it does not undergo any metabolism, thereby is eliminated in unchanged form in urine. The main cause of accumulation of this drug is due to renal failure as the metformin is eliminated unchanged. It can be extracted via dialysis from blood[6].

Lactic acidosis

Lactic acidosis is defined as an accumulation of the lactic acid or the lactate. This is secondary to various mechanisms like diabetes mellitus, glycogen storage disease, malignancy, salicylates and seizures. The lactic acid accumulation is seen in patients who already have impaired cardiac and liver, nephro and also respiratory functions.

It is a condition with a poor diagnosis and is serious. It occurs when there are excess amounts of lactic acids in blood and is a type of metabolic acidosis. It is basically categorized as anaerobic and aerobic. Anaerobic (TYPE A) type of lactic acidosis is due to tissue hypoxia which further results in the production of anaerobic lactic acid. The aerobic (TYPE B) type of lactic acidosis, there is increased production of lactic acid in absence of hypoxia.

Metformin Associated Lactic Acidosis (MALA) is a rare but classic side effect of metformin. It occurs due to overdose of metformin. The pathology of MALA is known to have the effects of anti hyperglycemic actions. The accumulation of metformin due to overdose or renal failure leads to more or stronger inhibition of mitochondrial complex 1 activity, thereby leading to reduction in the production of ATP and therefore the activation of AMP-K to compensate for the decrease in available energy. This causes either the stimulation of glycolysis followed by production of lactate or the stimulation of fatty acid beta oxidation followed by production of ketone bodies, which together are responsible for the release of lactate and ketone bodies in blood and are acidic. The risk of lactic acidosis depends on the balance between the production and elimination rates of lactate and ketone bodies. MALA refers to a condition where any patient who has developed lactic acidosis when he is being treated with metformin[7-10].

Epidemiological data

Epidemiological data on metformin-associated lactic acidosis (MALA) provide insights into the occurrence and risk factors associated with this rare but serious side effect of metformin therapy[11-12]. Here are some of the key points regarding the epidemiology of MALA:

Key Points	Epidemiology of MALA
1. Incidence of MALA	Rare event (<10 cases per 100,000 patient-years)
2.Renal Function	Major risk factor, incidence increases with declining kidney function
3. Age-Related Variations	Advanced age, especially with reduced renal function, is a risk factor
4. Comorbidities and Medications	Presence of comorbidities, interacting medications can increase risk
5. Duration of Metformin Use	Low risk during short-term use, higher with prolonged use in at-risk patients
6. Underreporting and Misdiagnosis	True incidence may be underestimated due to underreporting or misdiagnosis
7. Risk-Benefit Assessment	Healthcare providers weigh MALA risk against metformin's benefits

PATHOPHYSIOLOGY

The pathophysiology of metformin-associated lactic acidosis (MALA) is complex and involves several interrelated factors. The pathophysiology of Metformin-Associated Lactic Acidosis (MALA) involves several key steps:

1. Metformin Uptake and Accumulation: Metformin is absorbed in the gastrointestinal tract and reaches the bloodstream. It is primarily excreted unchanged in the urine. In individuals with normal renal function, metformin is efficiently cleared from the body. However, in cases of impaired renal function, metformin can accumulate in the body, leading to higher plasma concentrations.

2. Mitochondrial Dysfunction: Metformin is believed to inhibit complex I of the mitochondrial respiratory chain, a critical component of cellular energy production. This interference disrupts the flow of electrons through the chain, resulting in a decreased production of adenosine triphosphate (ATP), which is the primary energy currency of cells.

3. Shift toward Anaerobic Metabolism: Due to the inhibition of complex I and reduced ATP production, cells undergo a metabolic shift towards anaerobic glycolysis. This process does not require oxygen and results in the production of lactate from glucose.

4. Lactate Accumulation: Under normal circumstances, lactate produced during glycolysis is efficiently metabolized within the mitochondria. However, with impaired mitochondrial function caused by metformin, there is a reduced utilization of lactate, leading to its accumulation in the bloodstream[13-14].

5. Impaired Lactate Clearance: Metformin can also hinder hepatic gluconeogenesis, a primary pathway for lactate clearance. This means that not only is lactate production increased, but its clearance from the bloodstream is reduced, contributing to elevated lactate levels.

6. pH Disturbance and Acidosis: Elevated levels of lactate in the bloodstream lower the blood's pH, leading to a condition known as acidosis. Acidosis can disrupt various physiological processes and result in clinical symptoms associated with acidemia.

7. Hypoxia and Tissue Hypoperfusion: MALA can have systemic effects, such as reduced oxygen delivery to tissues and organs. This can occur due to impaired cardiac output and vasoconstriction, leading to tissue hypoxia and the potential for organ dysfunction. MALA is primarily driven by metformin's impact on mitochondrial function, leading to a cascade of events including lactate accumulation, impaired clearance, acidosis, and potential tissue hypoxia, particularly in individuals with impaired renal function. It is a rare but serious side effect associated with metformin

Mechanism of action of Metformin

Metformin is an oral medication commonly used to treat type 2 diabetes. Its primary mechanism of action involves several interconnected processes in the body[15]:

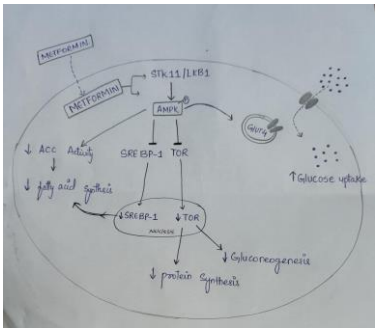
1. Glucose Lowering: Metformin primarily reduces blood glucose levels by decreasing the production of glucose in the liver (gluconeogenesis).It inhibits an enzyme called glucose-6-phosphatase, which is involved in the release of glucose from the liver into the bloodstream.By decreasing hepatic glucose production; metformin helps in lower fasting blood sugar levels.

2. Insulin Sensitivity: Metformin improves insulin sensitivity in peripheral tissues, such as muscle and fat cells.It enhances the uptake of glucose by these tissues, making them more responsive to insulin.This mechanism helps improve the utilization of glucose in the body and reduces insulin resistance.

3. Reduced Intestinal Glucose Absorption: Metformin may also decrease glucose absorption in the intestines. It can slow down the absorption of glucose from the digestive tract into the bloodstream, thereby contributing to lower post-meal blood sugar levels.

4. Metabolic Effects: Metformin can have various metabolic effects, including the reduction of free fatty acids in the blood.Lower levels of circulating free fatty acids can improve insulin sensitivity and reduce the risk of cardiovascular complications associated with diabetes.

5. AMPK Activation:



One of the key mechanisms of metformin involves the activation of an enzyme called AMP-activated protein kinase (AMPK).AMPK plays a central role in regulating cellular energy balance.Activation of AMPK by metformin leads to increased glucose uptake in cells, enhanced fatty acid oxidation, and decreased gluconeogenesis.

Risk factors

Metformin-associated lactic acidosis (MALA) is a rare but potentially life-threatening side effect of metformin use. Risk factors for MALA can be divided into patient-related and metformin-related factors:

Patient related factors

1. Impaired Renal Function:
   - Impaired kidney function, often indicated by a reduced glomerular filtration rate (GFR), is one of the most significant risk factors for MALA. The kidneys are responsible for excreting metformin, and if they are not functioning properly, metformin can accumulate in the bloodstream.
2. Advanced Age:
   - Older individuals are more prone to MALA due to age-related declines in renal function. The elderly may be less efficient at clearing metformin from their bodies.
3. Comorbidities:

Certain medical conditions, such as congestive heart failure, liver disease, or chronic obstructive pulmonary disease (COPD), can increase the risk of MALA. These conditions may impair oxygen delivery to tissues and contribute to lactate buildup.

4. Dehydration:

Dehydration can decrease blood flow to the kidneys, further impairing metformin clearance and potentially leading to MALA

Metformin related factors

1. High Doses: The use of high doses of metformin, especially above the recommended maximum daily dose, increases the risk of MALA.

2. Duration of Use: Prolonged use of metformin, particularly when other risk factors are present, can elevate the risk of MALA.

3. Concurrent Medications: Certain medications, such as contrast agents used in medical imaging procedures, can interact with metformin and exacerbate its effects, potentially increasing the risk of MALA.

4. Excessive Alcohol Intake: Excessive alcohol consumption can affect liver function and may interact with metformin, increasing the risk of MALA.

It's essential for healthcare providers to carefully assess patients for these risk factors before prescribing metformin. Regular monitoring of renal function is typically recommended for individuals taking metformin, especially in those with underlying risk factors. If any symptoms of lactic acidosis, such as muscle pain, weakness, or difficulty breathing, occur, prompt medical attention is crucial. The benefits of metformin in managing diabetes should be weighed against the potential risks, especially in patients with multiple risk factors for MALA.

Clinical manifestations

It occurs when there is an accumulation of lactic acid in the blood due to impaired lactate clearance. Some of the clinical manifestations of MALA include:

- Abdominal pain: Patients may experience diffuse or localized abdominal pain, which can be severe.
- Nausea and vomiting: These symptoms are common in MALA and may be associated with the presence of lactic acidosis.
- Reduced level of consciousness: As lactic acidosis progresses, patients may become lethargic, confused, or even have a loss of consciousness.
- Hyperventilation: Patients may exhibit rapid breathing and deep respirations in response to metabolic acidosis.
- Hypotension: MALA can lead to low blood pressure, which may result in dizziness or fainting.
- Cold and clammy skin: As the body tries to compensate for the metabolic acidosis, the skin may become cool and moist.
- Ileus: MALA can cause gastrointestinal dysmotility, leading to symptoms such as bloating and constipation.
- It is important to note that these symptoms may also be present in other conditions, so a thorough evaluation is necessary to confirm the diagnosis of MALA. Prompt recognition and management of MALA is crucial to prevent further complications.

CASE PRESENTATION

Metformin-Associated Lactic Acidosis in Sarika-Patient Identification: Name: sarika gupta Age: 32 years Gender: Female Occupation: Software Engineer Chief Complaint: Severe abdominal pain and shortness of breath.

Presenting History

Sarika, a 32-year-old female software engineer, presents to the emergency department with complaints of severe abdominal pain and shortness of breath for the past 12 hours. She reports feeling increasingly fatigued and developed a vague sense of unease. Sarika has a known medical history of type 2 diabetes mellitus, being treated with metformin (oral hypoglycemic agent) for the past 4 months.

Medical History

Type 2 diabetes mellitus diagnosed 5 years ago - No significant past medical or surgical history - Non-smoker, occasional alcohol consumption - Family history: Father with hypertension
Medication History: - Metformin 850 mg twice daily

Clinical Findings

Vitals: - Blood pressure: 135/80 mmHg - Heart rate: 102 beats per minute - Respiratory rate: 24 breaths per minute - Oxygen saturation: 91% on room air

Physical Examination

Anxious appearance,Abdomen: Tenderness in the epigastric region, guarding, and distention - Respiratory: Increased work of breathing with decreased air entry in both lung fields - Cardiovascular: Regular heart sounds, no murmurs or gallops - Neurological: Fully conscious and alert

Diagnostic Evaluation

Blood tests: - Complete blood count: Normal - Comprehensive metabolic panel: - Blood glucose: 110 mg/dL (within normal limits) - Serum lactate: 8.5 mmol/L (elevated) - pH: 7.24 (acidemic) - Anion gap: 20 mEq/L (increased) - Arterial blood gas: pH 7.24, pCO2 32 mmHg, HCO3 15 mEq/L - Urine analysis: Negative for ketones and glucose - Electrocardiogram: Sinus tachycardia

Assessment

Based on the clinical history, physical examination, and laboratory findings, the following diagnoses are considered:
1. Metformin-associated lactic acidosis (MALA)
2. Diabetic ketoacidosis (DKA) - less likely due to absence of hyperglycemia and ketonuria
3. Acute abdomen - differential diagnosis includes pancreatitis, gastrointestinal obstruction, or perforation

Plan of action

Immediate resuscitation and stabilization

Administer oxygen via nasal cannula to maintain oxygen saturation above 94% - Establish intravenous access with two large-bore peripheral catheters - Start fluid resuscitation with normal saline at 1-2 liters bolus as needed - Continuous cardiac monitoring and pulse oximetry - Consult a specialist team including an endocrinologist, gastroenterologist, and intensivist - Discontinue metformin immediately - Correct acidosis by providing intravenous sodium bicarbonate if necessary - Obtain further imaging (e.g., abdominal ultrasound or CT scan) to evaluate the cause of acute abdomen - Monitor serum lactate levels and renal function closely - Initiate insulin therapy as per the guidance of the endocrinologist - Consider dialysis for refractory lactic acidosis or renal failure

Discussion on case presentation

Sarika, a 32-year-old female with a history of type 2 diabetes mellitus, presented with symptoms suggestive of metformin-associated lactic acidosis (MALA). She exhibited classic features of abdominal pain, shortness of breath, and increased lactate levels. MALA is a rare but serious complication of metformin therapy, especially in patients with underlying renal dysfunction or other risk factors. The early recognition and prompt management of MALA are essential to prevent organ dysfunction and mortality.

Safety guidelines

Here are some guidelines for metformin-associated lactic acidosis:

- 1.Early recognition: Be aware of the signs and symptoms of lactic acidosis, such as rapid breathing, nausea, vomiting, abdominal pain, muscle weakness, and fatigue.

- 2. Stop metformin: Discontinue metformin immediately if lactic acidosis is suspected or confirmed.
- 3. Supportive care: Provide appropriate supportive measures including intravenous fluids, oxygen therapy, and close monitoring of vital signs.
- 4. Correct underlying conditions: Identify and address any underlying causes contributing to lactic acidosis, such as dehydration or kidney dysfunction.
- 5. Renal function assessment: Evaluate renal function before initiating metformin therapy and monitor it regularly thereafter.
- 6. Avoid metformin in high-risk patients: Use caution when prescribing metformin to patients with conditions that may increase the risk of lactic acidosis, such as renal impairment or liver disease.
- 7. Communication with healthcare provider: Promptly inform a healthcare professional if any signs or symptoms of lactic acidosis occur.

II. DISCUSSION

Metformin associated lactic acidosis. The laboratory investigations of the patient are as follows:

Diagnostic evaluation	Values
Blood glucose	110mg/d
Serum lactate	8.5mmol/lit
Ph	7.24
Anion gap	20mEq/l
Pco2	32mmHg
Hco3	15Eq/l
Urine analysis	Negative for ketone and glucose
ECG	Sinus tachycardia

Biguanide is an antidiabetic medication and is a compound which has been synthesized from two guanidines. Metformin is a biguanide and has a good oral bioavailability. The distribution of it follows two compartment models. Metformin is used alone or can be used with other oral hypoglycemic agents. It has effects on reducing hyperglycemia and blood pressure, and also improves the lipid profile.Metformin associated lactic acidosis is a rare but serious condition. As mentioned above, a female patient was admitted with complaints of shortness of breath and severe abdominal pain. The laboratory investigations of the patient are as follows.

III. CONCLUSION

The condition or situation discussed here is rare but serious, associated with Metformin.There is also important differences find out between type A and type B. Type A results from tissue hypoxia and Type B results due to over production of lactic acidosis; thereby conclude that the MALA is a Type B lactic acidosis. Moreover on the basis of case presentation and by observing several case reports, it can understand that the hepatic, renal, cardiovascular issues can progress the accumulation of lactic acidosis in metformin therapy.

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