

Side Effects and Adverse Reactions of Metformin

Introduction

Metformin is generally considered safe and well-tolerated for most patients with type 2 diabetes. However, like all medications, it can cause a range of side effects from mild to severe. This comprehensive review examines the common, uncommon, and rare adverse reactions associated with metformin use, with particular attention to the potentially life-threatening complication of lactic acidosis.

Common Gastrointestinal Side Effects

The most prevalent adverse reactions to metformin are gastrointestinal (GI) disturbances, affecting up to 30% of patients who take the medication. These GI effects include diarrhea, nausea, vomiting, abdominal discomfort, bloating, flatulence, and a metallic taste in the mouth (dysgeusia). These symptoms are typically dose-dependent and tend to occur most frequently during the initiation of therapy or when dosages are increased.

For many patients, these GI side effects are transient and resolve spontaneously as the body adjusts to the medication. Several strategies can help minimize these effects, including:

1. Starting with a low dose and gradually titrating upward
2. Taking metformin with meals rather than on an empty stomach
3. Using extended-release formulations, which have been shown to reduce GI intolerance compared to immediate-release versions
4. Temporarily reducing the dose if symptoms become severe, then slowly increasing it again

Despite these approaches, approximately 5% of patients find the GI side effects intolerable and discontinue the medication. For those who persist, symptoms often improve within a few weeks of starting treatment.

Vitamin B12 Deficiency

Long-term use of metformin has been associated with decreased vitamin B12 levels, which can lead to vitamin B12 deficiency. This effect is thought to occur due to interference with vitamin B12 absorption in the ileum. Studies suggest that 10-30% of patients taking metformin for extended periods may develop reduced vitamin B12 levels.

The risk of B12 deficiency increases with:

- Higher metformin doses
- Longer duration of therapy
- Advanced age
- Dietary factors (limited intake of B12-rich foods)
- Concomitant use of acid-suppressing medications

Symptoms of vitamin B12 deficiency may include fatigue, weakness, peripheral neuropathy, cognitive changes, and anemia. Healthcare professionals should carefully monitor patients on long-term metformin therapy, especially those with anemia or peripheral neuropathy. In some cases, supplementation of vitamin B12 may be necessary to prevent or treat deficiency.

Hypoglycemia

Unlike many other antidiabetic medications, metformin alone rarely causes hypoglycemia (low blood sugar) when used as monotherapy. This is because metformin does not stimulate insulin secretion. However, when combined with other glucose-lowering medications such as sulfonylureas, insulin, or meglitinides, the risk of hypoglycemia increases significantly.

Symptoms of hypoglycemia may include shakiness, dizziness, sweating, hunger, irritability, confusion, tachycardia, and in severe cases, loss of consciousness. Patients should be educated about recognizing and managing hypoglycemic episodes, particularly when metformin is used in combination therapy.

Lactic Acidosis

Metformin carries a black box warning for lactic acidosis, an infrequent but potentially fatal adverse effect with an incidence rate of approximately 1 in 30,000 patients. Lactic acidosis occurs due to lactate accumulation in the body, which cannot be eliminated quickly, leading to metabolic acidosis.

This serious condition is characterized by a decrease in blood pH and nonspecific signs and symptoms such as:

- Malaise and fatigue
- Muscle pain (myalgia)
- Respiratory distress
- Somnolence
- Abdominal discomfort
- Elevated lactate levels
- Increased anion gap

Several risk factors contribute to developing lactic acidosis while on metformin therapy:

- Hepatic impairment
- Renal dysfunction (especially with $\text{eGFR} < 30 \text{ mL/min/1.73m}^2$)
- Advanced age (≥ 65 years)
- Recent surgery or procedures requiring contrast agents
- Hypoxic states (heart failure, respiratory failure, shock)
- Excessive alcohol consumption

These risk factors either lower the blood's pH or hinder proper lactate elimination.

Although lactic acidosis is rare, it can lead to severe consequences including hypotension, hypothermia, and death if not promptly recognized and treated. Treatment typically involves discontinuation of metformin, supportive measures in a hospital setting, and prompt hemodialysis.

Less Common Side Effects

Less commonly, patients may experience:

- Chest discomfort
- Headache
- Diaphoresis (excessive sweating)
- Weakness
- Rhinitis (nasal inflammation)
- Rash or skin reactions
- Discoloration of the fingernails or toenails
- Joint pain
- Flu-like symptoms

Some patients may also experience changes in taste perception, with a metallic taste being the most commonly reported. While these side effects are generally not serious, they can affect quality of life and medication adherence.

Rare Side Effects

Rare side effects of metformin include:

- Behavior changes similar to being drunk
- Difficulty concentrating
- Drowsiness
- Lack or loss of strength
- Restless sleep
- Megaloblastic anemia (related to B12 deficiency)
- Hepatic enzyme elevations

Drug Interactions

Specific drug interactions can raise the risk of lactic acidosis or enhance the hypoglycemic effect of metformin. Medications that may interact with metformin include:

1. Drugs that increase lactic acidosis risk:
2. Bupropion
3. Carbonic anhydrase inhibitors
4. Cephalexin
5. Cimetidine
6. Dolutegravir
7. Ethanol
8. Glycopyrrolate
9. Iodinated contrast agents
10. Lamotrigine
11. Ranolazine
12. Topiramate
13. Drugs that enhance the hypoglycemic effect:
14. Androgens
15. Alpha-lipoic acid
16. Salicylates
17. Selective serotonin reuptake inhibitors (SSRIs)
18. Quinolones
19. Prothionamide
20. Other antidiabetic agents

Healthcare providers should carefully monitor patients who are concurrently taking these medications along with metformin.

Special Populations and Considerations

Renal Impairment

Metformin is contraindicated in patients with severe renal dysfunction, defined as an estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73m². This limitation also applies to individuals with serum creatinine levels greater than or equal to 1.5 mg/dL in men and 1.4 mg/dL in women, or with abnormal creatinine clearance.

For patients with moderate renal impairment (eGFR 30-45 mL/min/1.73m²), the manufacturer's label recommends against initiating metformin therapy, although some researchers suggest a reduced dose of 500 mg daily with an evening meal may be considered.

Hepatic Impairment

The manufacturer recommends avoiding metformin therapy in patients with hepatic impairment due to the increased risk of lactic acidosis. Patients with liver disease may have impaired lactate metabolism, which can lead to lactate accumulation.

Elderly Patients

For individuals of advanced age (≥ 65 years), it is recommended to begin with a lower initial and maintenance dose as a precaution. This population may exhibit decreased renal function, making it crucial for physicians to adjust the dose based on a thorough assessment of renal health.

Surgical Procedures and Contrast Studies

Metformin dosing should be discontinued on the day of any surgery. Additionally, according to metformin's package insert, patients with a GFR < 60 mL/min/1.73m² or those receiving contrast intra-articularly should discontinue metformin before being administered iodinated contrast agents. Metformin may be resumed after the procedure once the patient's GFR has returned to normal.

Pregnancy and Breastfeeding

Metformin was previously categorized as a US FDA pregnancy category B drug. According to the American College of Obstetricians and Gynecologists (ACOG) guidelines, insulin

remains the preferred choice for managing gestational diabetes. However, metformin could be considered an alternative for cases involving non-compliance or technical challenges with insulin administration.

Metformin can be detected in breast milk, but breastfeeding is generally deemed acceptable as long as the relative infant dose remains below 10 mg/kg/day.

Conclusion

While metformin is generally considered safe and well-tolerated, awareness of its potential side effects is crucial for both healthcare providers and patients. Most adverse reactions are mild and transient, with gastrointestinal disturbances being the most common. The rare but serious risk of lactic acidosis necessitates careful patient selection and monitoring, particularly in those with renal or hepatic impairment, advanced age, or other risk factors.

Regular monitoring of renal function, vitamin B12 levels in long-term users, and awareness of drug interactions can help minimize adverse effects and optimize the safety profile of this widely used antidiabetic medication.

References

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