SHORT COMMUNICATION

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METFORMIN: WHEN TO DISCONTINUE IT BEFORE GENERAL ANESTHESIA?

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Abstract: Metformin is one of the main medications in the treatment of type 2 diabetes. Despite its widespread use, there are controversies surrounding the continuation of therapy with this drug during the perioperative period, mainly due to the risk of metabolic acidosis. The likelihood of developing metabolic acidosis associated with the use of metformin is very rare, but it increases in patients with impaired kidney function as well as in conditions of hypoperfusion and hypoxia.

There are differences between various recommendations regarding the use of metformin during the perioperative period. The widespread use of the drug, coupled with the lack of consistency in recommendations, should encourage efforts to standardise them, particularly for optimal metabolic control of surgical patients.

Keywords: metformin, metabolic acidosis, perioperative period

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OWN STUDY

Approximately 828 million adults worldwide suffer from diabetes [10]; among them, there are about 3 million patients in Poland, with 90% of these cases being type 2 diabetes. According to the guidelines of the Polish Diabetes Association [17], first-line medications for initiating pharmacological treatment in type 2 diabetes are sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide-1 (GLP-1) analogs, or metformin. Metformin is therefore the cornerstone of treatment for millions of patients worldwide. However, its use in the context of general anaesthesia and surgical procedures is controversial.

Metformin exerts its hypoglycemic effect through the following mechanisms:

- Inhibition of gluconeogenesis in the liver; this mechanism is mediated by the activation of AMP-activated protein kinase (AMPK), which decreases the activity of pyruvate carboxylase and phosphoenolpyruvate carboxykinase—enzymes involved in gluconeogenesis.
- Inhibition of complex I of the electron transport chain in mitochondria, which reduces ATP production, thereby increasing the AMP/ATP ratio. High AMP levels activate AMPK, which inhibits lipid synthesis and enhances glucose uptake in peripheral tissues.
- Increased sensitivity of peripheral tissues (e.g., muscles) to insulin, which enhances glucose uptake via glucose transporter type 4 (GLUT4).
- Reduction in the production of reactive oxygen species in mitochondria, which decreases oxidative stress associated with hyperglycaemia.
- Alteration of the gut microbiota composition, which improves glucose metabolism and may reduce inflammation.
- Inhibition of acetyl-CoA carboxylase (ACC), which reduces lipid synthesis, lowering LDL cholesterol and triglyceride levels [8,13,16].

The main concerns regarding the use of metformin in the perioperative period are the potential for lactic acidosis.

One of the mechanisms of metformin's action is the inhibition of mitochondrial glycerophosphate dehydrogenase (mGDP), which hinders the conversion of glycerol-3-phosphate to dihydroxyacetone phosphate (DHAP), consequently limiting gluconeogenesis from glycerol. Inhibition of mGDP also reduces the concentration of oxidized nicotinamide adenine dinucleotide (NAD+), thus limiting the conversion of lactate to pyruvate [2,9,13,14]. An increase in lactate levels may therefore be the result of either lactate accumulation in the serum (due to hypoxia, inhibition of oxidative metabolism, and reduced available ATP) or decreased lactate utilisation in the liver. Lactic acidosis can thus be divided into two types: Type A and Type B. Type A acidosis results from hypoperfusion and tissue hypoxia, while Type B lactic acidosis encompasses other causes, including intoxications, liver failure, inherited enzyme deficiencies, and may also be a consequence of drug use, including metformin [1].

Metformin-associated lactic acidosis (MALA) can be suspected in a patient who has been receiving metformin and presents with acidosis and a high anion gap, and it can be confirmed if lactate levels exceed 5 mmol/L. The incidence of this disorder is estimated to be 3 to 6 cases per 100,000 patients. Risk factors for the development of MALA include conditions in which metformin elimination by the kidneys is reduced: kidney failure from any cause, use of histamine H2 receptor antagonists, use of ribociclib, and excessive alcohol consumption [6]. Metformin is excreted by the kidneys, so conditions that lead to a reduced glomerular filtration rate (eGFR) are the primary risk factors for the accumulation of metformin in the body and the occurrence of its toxicity [15]. Therefore, it can be assumed that the likelihood of MALA occurring in normally functioning patients, i.e., those who are not critically ill and without risk factors, would be virtually incidental. However, it should be noted that the mortality rate in cases of MALA is high, ranging from 10.8% in the United Kingdom to 36.2% in Thailand [15].

According to the recommendations of the manufacturers of metformin preparations (Avamina®, Glucophage®, Metformax®, Siofor®) included in the product characteristics, the administration of metformin must be discontinued immediately before a surgical procedure performed under general, spinal, or epidural anesthesia, and treatment can be resumed no earlier than 48 hours after the procedure or after oral nutrition is resumed, and after a re-evaluation of kidney function to confirm that it is stable. In practice, it is often recommended to discontinue metformin 24 to 48 hours before surgery.

In light of the information provided in the product characteristics, it is difficult to assume that discontinuing the drug 24–48 hours before the procedure is equivalent to discontinuing it "immediately before surgery." However, such recommendations have been published not only regarding the perioperative period [3,7] but also for patients scheduled for a PET scan using 18-fluorodeoxyglucose [4]. Some authors, however, argue that

the evidence for the effectiveness of such an approach is weak and that metformin is a safe drug in the perioperative period, provided that the patient has normal kidney function and does not use contrast agents.

Normal creatinine levels usually range from 0.7 to 1.3 mg/dl for men and from 0.6 to 1.1 mg/dl for women, although these should be assessed according to the reference values of the laboratory performing the test. The GFR value is calculated, with the normal value being ≥ 90 ml/min/1.73 m^2, and depends on factors such as age, sex, and muscle mass. It should be noted that doubling the serum creatinine concentration (even if the measured values are within the normal range) corresponds roughly to a 50% reduction in GFR. The biochemical assessment of kidney damage is complex; in the most rigorous approach, any creatinine concentration that exceeds the upper limit of the laboratory's reference values can be considered abnormal. According to Pontes et al., metformin administration should be discontinued if (1) kidney damage is present, as assessed by GFR and creatinine concentration, (2) contrast agent use is planned, or (3) there is a risk of acute kidney failure; in such cases, metformin should not be administered on the day of surgery and for the following 48 hours [11]. According to French guidelines, for planned major surgeries, metformin administration should be discontinued on the evening before the procedure, and resumed 48 hours after the surgery, once it has been confirmed that the patient's kidney function is normal. For minor procedures or those performed on an outpatient basis, metformin should be continued unless the patient has kidney failure [5]. Belgian authors present a similar position: for same-day procedures, continuation of metformin is recommended, except for patients with impaired kidney function or those who are scheduled to receive contrast agents, non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, or angiotensin II receptor antagonists. For major procedures, discontinuation of metformin is recommended the evening before the surgery. In both cases, metformin can be resumed once the patient returns to oral nutrition and has normal kidney function [12].

In summary, the lack of consensus regarding metformin use in the perioperative period stems from differences in available recommendations, individual medical issues of patients, and the type of planned surgery. However, there are situations where metformin therapy can be safely continued, and others where discontinuation is recommended to minimize the risk of metabolic acidosis. Metformin treatment can be continued if (1) the patient has normal kidney function, (2) the planned surgical intervention is minor or is to be performed on an outpatient basis, and (3) no contrast agents or other medications that may affect metformin elimination are used. Decisions should always be made individually, considering the patient's clinical condition, the planned procedure, and the risk of complications. In doubtful situations, metformin administration should be discontinued for 48 hours. Such an approach will ensure maximum patient safety while maintaining optimal metabolic control during the perioperative period.

AUTHORS' DECLARATION:

Study Design: Dariusz Tomaszewski. Data Collection: Dariusz Tomaszewski. **Manuscript preparation:** Dariusz Tomaszewski. The author declares that they have no conflicts of interest.

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