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Use of metformin in patients who require intravascular administration of a contrast agent

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Abstract

Metformin is a drug that has been widely used around the world for many years. Due to its properties, metformin is used in the treatment of carbohydrate disorders (in type 2 diabetes, prediabetes) and in insulin resistance syndromes (including polycystic ovary syndrome). Many patients using metformin, due to complications of carbohydrate metabolism disorders, including cardiovascular complications or other accompanying diseases, require cardiological or radiological diagnostics related to the administration of a contrast agent.

The aim of this study is to summarize the recommendations regarding the use of metformin before procedures involving the use of contrast agents and to share our own experience in this area, based on observations of a large group of patients with cardiological diseases hospitalized at the Silesian Centre for Heart Diseases in Zabrze. **(Endokrynol Pol 2022; 73 (6): 913–916)**

Key words: *metformin; contrast agents*

Introduction

Metformin is a drug that has been widely used in the treatment of type 2 diabetes since the 1950s. Since then, its mechanisms of action and all kinds of side effects that may occur with metformin therapy have been discovered. After oral administration of the short-acting form, 50-60% of the drug is absorbed from the gastrointestinal tract, reaching maximum concentration after about 2.5 hours. Approximately 20-30% of metformin is excreted in the faeces. The dose and the administration of metformin with a meal affect the absorption of the drug and its duration of action, although this is not of great importance for the clinical effects [1]. There is wide interindividual variability in the pharmacokinetics of metformin. The plasma metformin concentration ranges from 54 to 4133 ng/mL, which is probably related to the different expression of genes encoding transmembrane transporters for metformin [organic cation transporter (OCT) and multidrug and toxin extrusion (MATE)], thanks to which, unchanged metformin is transported from the intestines to the plasma and then to the target cells [2, 3]. Metformin is excreted unchanged in the urine by glomerular filtration and tubular secretion. The most likely factors involved in the elimination of metformin are the proteins OCT2 as well as MATE1 and MATE2-K located in the renal tubular cells. Polymorphism of genes encoding metformin transport membrane proteins or the influence of other drugs on these proteins (e.g. inhibition of the MATE protein by cimetidine) may have a direct impact on the pharmacokinetics of metformin, the variability of the drug response, and the toxic effect of the drug in a particular patient [2, 3]. In impaired renal function with decreased creatinine clearance, renal clearance of metformin is also decreased, leading to a prolonged metformin half-life and increased plasma levels. This mechanism may lead to the development of lactic acidosis in patients taking metformin and suffering from acute or chronic kidney disease with significantly reduced glomerular filtration rates [1, 3].

One of the mechanisms of action of metformin is to inhibit hepatic gluconeogenesis by blocking mitochondrial glycerophosphate dehydrogenase (mGDP), an enzyme that links carbohydrate and lipid metabolic pathways. The action of metformin on the mGDP enzyme hinders the conversion of glycerol-3-phosphate to dihydroxyacetone phosphate (DHAP) and thus blocks gluconeogenesis from glycerol. Due to the influence of metformin on this part of the metabolic pathway, the concentration of oxidized nicotine adenine dinucleotide (NAD+) is decreased, which leads to impaired

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conversion of lactate to pyruvate. Ultimately, intracellular lactate accumulation occurs, with the potential to develop lactic acidosis. In healthy people, the accumulation of lactate does not pose a health risk because it is a substrate for hepatic gluconeogenesis.

If the recommended doses of the drug are used and the contraindications to metformin therapy are observed, the amount of intracellularly accumulated lactate is harmless. However, it should be remembered that all diseases leading to the overproduction of lactate in the situation of tissue hypoxia, when anaerobic respiration predominates (e.g. respiratory failure, circulatory failure) in combination with the use of metformin, may lead to its excessive accumulation and the development of lactic acidosis [1].

Therefore, for the safety of patients, daily doses of metformin used in the treatment of carbohydrate metabolism disorders have been determined, making the dose dependent on the estimated glomerular filtration rate (eGFR). The use of metformin in patients with eGFR 30–59 mL/min/1.73 m^2 is considered safe when doses are appropriately reduced. A dose limitation of metformin is recommended to a maximum of 2000 mg/day for eGFR 45–60 mL/min/1.73 m^2 and a maximum of 1000 mg/day for eGFR 30–44 mL/min/1.73 m^2. In patients with eGFR 30–59 mL/min/1.73 m^2, metformin levels remain within the therapeutic range. In patients with eGFR < 30 mL/min/1.73 m^2, the administration of metformin is contraindicated [1, 5]. When using metformin in the form of prolonged-release tablets, the maximum daily dose of 2000 mg can be used in patients with eGFR up to 45 mL/min/1.73 m^2. For eGFR values of 30–44 mL/min/1.73 m^2, the daily dose should be reduced to 1000 mg. When initiating treatment with metformin, both with prolonged-release and faster-release metformin tablets in patients with eGFR < 60 mL/min/1.73 m^2, factors that may increase the risk of lactic acidosis should be considered. The starting dose should not exceed half of the maximum dose [1]. The recommendations of the Polish Diabetes Society formulate slightly different guidelines for metformin dosing in individual groups of patients with type 2 diabetes and reduced eGFR. The use of metformin in patients with eGFR 45–60 mL/min/1.73 m^2 is considered safe without the need for dose adjustment; therefore, a maximum of 3000 mg of metformin can be maintained in this group of patients. Only a decrease in eGFR below 45 mL/min/1.73 m^2 and the maintenance of eGFR in the range of 30–44 mL/min/1.73 m^2 should force a physician to reduce the dose to 1000 mg/day [7]. Similar restrictions are included in the Kideny Disease: Improving Global Outcomes (KDIGO) recommendations. However, this document emphasizes that metformin dose adjustment is necessary when eGFR is < 45 mL/min per 1.73 m^2, but also in some patient groups when eGFR is 45–59 mL/min per 1.73 m^2. This applies to patients with diseases that predispose to tissue hypoperfusion and hypoxaemia. It should be noted that, contrary to our Polish recommendations in the recommendations of KDIGO, the maximum daily dose of metformin is initially lower, at 2550 mg and, in the case of the long-acting dose, 2000 mg [7].

A safe dose of metformin therefore depends on the function of the kidneys. All causes of acute renal failure or a decrease in glomerular filtration rate will have a direct influence on the dose of this medicine to be taken. The concern about kidney damage from the iodine contrast agent is justified. Free iodine released from the contrast medium has a direct cytotoxic effect on endothelial cells and the nephron tubule. Cell damage leads to oxidative stress and the formation of free radicals. The production of free radicals and reactive oxygen species (ROS) consumes nitric oxide (NO) and consequently reduces its protective vasodilatory effect. Persistent vasoconstriction, which can last for hours, reduces the glomerular filtration rate (GFR) and causes hypoperfusion of the renal medulla. The lack of an adequate blood supply leads to cellular hypoxia and, in a vicious circle, further damage to the glomeruli and renal tubules. In addition to the cytotoxic effect, water-soluble contrast agents as hyperosmolar substances, when passing through the tubules, draw water from the environment of lower osmolarity, which leads to an increase in pressure in the renal tubules. With an increase in the tubular pressure, the interstitial pressure increases, additionally exacerbating the hypoperfusion of the renal medulla caused by the previously discussed mechanism [8].

Post-contrast kidney injury, also known as CIN, is defined as an increase in serum creatinine concentration by at least 25% or an increase in serum creatinine concentration by ≥ 0.5 mg/dL in relation to the value before administration of the contrast medium, assessed within 24–48 hours after its administration [8]. Continued use of metformin in such a case may result in the development of lactic acidosis.

Recommendations for the use of metformin in patients receiving contrast media

Recommendations regarding the intravascular administration of contrast agents in patients using metformin can be found in the summary of product characteristics. Due to the risk of contrast medium administration in the form of post-contrast nephropathy, the risk of metformin accumulation in the body and thus

the risk of lactate accumulation and the development of lactic acidosis is significantly increased. Therefore, the producers of metformin recommend discontinuing the drug before the test (ed. — without specifying the necessary time interval) and not using it for 48 hours after the test. Resumption of drug use is possible after this time, provided that renal function is reassessed and found to be stable [1].

Until recently, the guidelines of scientific societies regarding the need to discontinue metformin before intravascular administration of contrast media were very strict [9, 10]. Currently, the guidelines have become less restrictive due to studies and meta-analyses that have shown that the risk of lactic acidosis with metformin is very low and associated more with the underlying disease and possible comorbidities than with the drug's effects [11–13].

Documents that contain recommendations for the use of metformin and the administration of contrast agents include the American College of Radiology (ACR) Manual on Contrast Media of 2021 and the European Society of Urogenital Radiology (ESUR) guidelines on contrast agents. They show that patients taking metformin are no more likely to develop acute renal failure after iodine contrast than other patients [14, 15].

The Contrast Media Safety Committee (CMSC) updated its recommendations based on the latest Food and Drug Administration (FDA) [16] recommendations and ACR and Radiological Society of the Netherlands (RSTN) guidelines. They clearly show that in patients with a baseline eGFR > 30 mL/min/1.73 m^2 and no evidence of acute kidney injury, normal metformin intake should be continued during the intravascular administration of the contrast agent. In patients with eGFR < 30 mL/min/1.73 m^2 or with acute kidney injury, metformin should be discontinued from the time of intravascular injection, then eGFR should be assessed within 48 hours, and metformin should be resumed based on the eGFR value [15, 17].

Therefore, the discontinuation of metformin after contrast therapy has been relaxed and now only applies to patients with eGFR < 30 mL/min/1.73 m^2 receiving contrast intravenously or intra-arterially but with second-pass renal function. In patients on metformin therapy, who are scheduled to receive an intra-arterial contrast agent with a renal first-pass effect or in acute renal failure, metformin should be discontinued regardless of eGFR. First-pass renal exposure is a situation in which a contrast agent is administered to the left heart, thoracic or abdominal aorta above the origin of the renal arteries or directly to the renal arteries. In these cases, the contrast agent enters the kidneys undiluted. A renal second-pass effect is the situation where the contrast agent reaches the renal arteries after dilution in the pulmonary or peripheral circulation, e.g. after administration to the right heart, pulmonary artery, carotid, subclavian, coronary, mesenteric, or aorta below renal arteries [14]. The provision regarding the withholding of metformin administration before contrast medium administration in the case of eGFR lower than 30 mL/min/1.73 m^2 seems to be a dead recommendation, as the use of the drug is contraindicated in such a situation. The situation is similar in patients with acute renal failure. In this case, we also do not use metformin as an antihyperglycaemic drug. Therefore, there remains a group of patients in whom metformin is used, and the administration of an iodine-based contrast agent intraarterially with the first-pass renal effect is planned. In these patients, we should discontinue the drug before testing with a contrast agent, regardless of eGFR, perform a creatinine test within 48 hours, and return to its use when the eGFR value does not change significantly [14].

There is much less information on the administration of gadolinium contrast agent. In the ACR guidelines, the team of experts did not recommend discontinuation of metformin before contrast medium administration when the amount of administered gadolinium-based contrast material is within the usual dose range of 0.1 to 0.3 mmol per kg body weight [15]. The ESUR guidelines recommend that metformin should not be discontinued during administration of the gadolinium contrast agent because the risk of post-contrast acute kidney injury is very low [14].

Based on our own experience, we analysed the issue of metformin use in patients undergoing cardiological procedures with intravascular administration of an iodinated contrast agent. Unpublished data from the Polish Registry of Acute Coronary Syndromes (PL-ACS) provided information about patients using oral antihyperglycaemic drugs, including metformin, who underwent coronary angiography (procedure with coronary contrast agent administration). Of 154,363 patients with ACS, coronary angiography, and diabetes, data on oral antidiabetic drugs were available for 18,633 patients, of whom 11,580 were treated with metformin. In 9.8% of patients in this group, contrast-induced nephropathy (CIN) was observed, i.e. an increase in creatinine by 25% or by 0.5 mg/dL after contrast administration. Data on lactic acidosis were not included in the registry; however, the fact that there were no in-hospital deaths in the above-mentioned population potentially excludes the occurrence of an acute complication in the form of lactic acidosis. It should be noted that some of the hospitalized patients were in a serious health condition, with heart failure resulting from acute myocardial ischaemia, which is a factor contributing to the development of lactic acidosis.

Conclusions

The problem of using and discontinuing metformin in the period preceding the administration of the contrast agent and after its intravascular administration is still unresolved. There are no randomized clinical trials unequivocally defining when metformin should not be used when an intra-arterial or intravenous contrast medium is planned. Based on the characteristics of the medicinal product of metformin, the drug should be discontinued before and restarted at the earliest 48 hours after administration of an iodinated contrast agent, but after prior assessment of the creatinine concentration and assessment of the glomerular filtration rate. The recommendations of the ESUR, ACR, and CMSC, and our own observations in our centre where patients with heart failure, with acute coronary syndromes and concomitantly using metformin, are subjected to treatments with iodine contrast agent, allow us to liberalize the recommendations regarding its use. Discontinuation of metformin is not recommended in patients with eGFR > 30 mL/min/1.73 m^2 prior to administration of an iodine-based contrast agent. The only patients who should discontinue the drug are those with acute renal failure or those in whom it is necessary to administer a contrast agent to the left heart, thoracic or abdominal aorta above the origin of the renal arteries or directly to the renal arteries, i.e. in the situation of the first-pass renal process. According to our observations, the most important issue regarding the use of metformin is to estimate the concentration of creatinine and glomerular filtration 48 hours after the procedure using an iodine-based contrast agent and adjust the metformin dose to these values, as well as adequate hydration of the patient before and after the administration of the contrast agent.

EXPERT OPINION

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