OPIS PRZYPADKU / CASE REPORT
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Metformin-induced diarrhea – case report
Biegunka wywołana metforminą – opis przypadku

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Streszczenie

Wstęp. Metformina jest lekiem pierwszego wyboru w przypadku rozpoczęcia leczenia farmakologicznego cukrzycy typu 2. Za najczęstsze działania niepożądane metforminy uznaje się zaburzenia ze strony przewodu pokarmowego. Spektrum powikłań obejmuje biegunkę, zgagę, nudności, wymioty, wzdęcia, ból brzucha i zaparcia. Nasilenie oraz częstość występowania tych objawów jest bardzo zróżnicowana. Dotyczą one przede wszystkim kobiet oraz osób w wieku podeszłym i zazwyczaj występują na krótko po rozpoczęciu terapii metforminą. Powikłania tego rodzaju, znacząco wpływają na jakość życia pacjenta i stanowią wyzwanie terapeutyczne, gdyż pogarszają współpracę pacjenta z lekarzem, stosowanie się pacjenta do zaleceń oraz ograniczają osiągnięcie optymalnej dawki leku. ***Materiał i metody***. Przedstawiamy przypadek 67-letniego pacjenta, u którego w trakcie leczenia metforminą wystąpiły działania niepożądane w postaci biegunki i bólu brzucha. ***Wyniki***. Objawy ustąpiły po zmianie sposobu dawkowania leku. ***Wnioski***. Opisany przypadek potwierdza ryzyko wystąpienia działań niepożądanych w postaci zaburzeń żołądkowo-jelitowych jako następstw terapii metforminą. *(Farm Współ 2021; 14: 64-67)* doi: 10.53139/FW.20211409

Słowa kluczowe: metformina, działania niepożądane leków, zaburzenia żołądkowo-jelitowe

Summary

Background. Metformin is the drug of the first choice when initiating pharmacological treatment in type 2 diabetes. The most common side effects of metformin are gastrointestinal disorders. The spectrum of complications includes diarrhea, heartburn, nausea, vomiting, gas, abdominal pain, and constipation. The severity and frequency of these symptoms vary widely. They mainly affect women and elderly patients and usually occur shortly after starting metformin therapy. Complications of this type significantly affect the patient's quality of life and constitute a therapeutic challenge, as they worsen the patient-doctor cooperation, patient compliance and limit the achievement of the optimal dose of the drug. ***Material and methods***. We describe a case report of a 67-year-old patient who experienced an adverse reaction of diarrhea and abdominal pain during the therapy with metformin. ***Conclusions***. The described case confirmed the risk of adverse reactions in the form of gastrointestinal disorders due to metformin therapy. *(Farm Współ 2021; 14: 64-67)* doi: 10.53139/FW.20211409

Key words*: Metformin, adverse drug reaction, gastrointestinal disorders*

Introduction

Metformin is the most widely used glucose-lowering agent worldwide, applied in the treatment of patients with type 2 diabetes. It is a dimethylbiguanide originating from *Galega officinalis*, recognized to lower blood glucose concentrations in animals in the 1920s, and then studied in humans by Jean Sterne in the 1950s under the name "Glucophage" [1]. According to the recommendations of the Polish Diabetes Association of 2020 and other scientific societies, metformin should be the drug of the first choice when initiating pharmacological treatment of type 2 diabetes unless it is contraindicated or not tolerated. In accordance with these recommendations, treatment with metformin should be continued practically until the end of life, regardless of the subsequent introduction of other drugs, including insulin [2]. Metformin is considered a safe drug. No symptoms of damage to internal organs have been found with long-term use of this drug in therapeutic doses. Nonetheless, adverse

reactions (ADR- adverse drug reaction) associated with metformin are common and mainly related to the digestive system. The most common ADRs to metformin are gastrointestinal adverse events (AEs) and lactic acidosis. Gastrointestinal manifestations include nausea, flatulence, abdominal pain, diarrhea, loss of appetite and a metallic taste in the mouth. These symptoms are dose-dependent, relatively transient and usually occurring at the beginning of treatment. They may resolve spontaneously, but sometimes patients require taking the medication with or immediately after a meal, slowly increasing the dose or switching to an extended-release formulation [3-4].

Case report

A 67-year-old patient reported to the family doctor (an online consultation) with diarrhea and abdominal pain that lasted for two weeks. The patient treated those symptoms for two days with medicinal charcoal (2 g/day) and then with loperamide (8-10 mg/day) and drotaverine (120 mg/day). After a week, the patient started taking a probiotic containing *Saccharomyces boulardi* and electrolytes (glucose, potassium and sodium). For ten years, the patient has been taking a safe and effective antihypertensive therapy: amlodipine (10 mg/day), ramipril (10 mg/day), indapamide (1.5 mg/day). The results of laboratory tests performed a month ago (fasting glucose > 126 mg/dl, random glucose > 200 mg/dl) and symptoms (increased diuresis, increased thirst, weakness and sleepiness) indicating disturbances in carbohydrate metabolism resulted in the addition of metformin 1000 mg/day in the evening. Following the online consultation, the patient was instructed to take metformin 500 mg twice daily with or shortly after a meal. Dosage modification resolved the gastrointestinal symptoms.

Discussion

Metformin, an efficacious and safe glucose-lowering drug (it can lower fasting and postprandial plasma glucose), is being used worldwide for more than 60 years in patients with type 2 diabetes. It is known for its high effectiveness in HbA1c lowering and the fact that it does not stimulate insulin secretion and, therefore, does not increase the risk of hypoglycemia. Thus, metformin is recommended worldwide in all guidelines for the management of diabetes- in patients with newly diagnosed diabetes as a monotherapy or in combination with other antidiabetic drugs [5]. The main mechanisms underlying metformin's antidiabetic action include: 1) reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis, 2) increase in insulin sensitivity in muscles, enhancing peripheral glucose uptake and consumption, 3) delay of the glucose absorption in the intestine. Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Moreover, it increases the transport capacity of all known types of glucose transporters (GLUT). Metformin has also been associated with stabilization or moderate weight loss in a clinical trial. In humans, independently of its action on glycaemia, metformin has favorable effects on lipid metabolism [6]. According to the recommendations of the Polish Diabetes Association of 2020, metformin should be the drug of the first choice when initiating pharmacological treatment in type 2 diabetes, unless it is contraindicated or not tolerated. When the monotherapy at the maximum recommended or tolerated dose becomes insufficient to achieve or maintain the HbA1c target, a second oral drug, a GLP-1 receptor agonist or basal insulin should be added [2]. Moreover, over the years, it has been observed that metformin can be applied not only in diabetic patients. People suffering from coronary heart disease, heart failure, chronic kidney disease, obesity and even cancers (prevention and treatment of (i.a) breast cancer, endometrial cancer, colorectal cancer, melanoma) may also benefit from metformin therapy. Metformin acts through different signaling pathways to contribute to different effects, but not all of these mechanisms are recognized yet [7]. The orally administered metformin half-life is relatively short, between 3 to 4 h (maximum plasma concentration is achieved in approximately 2.5 hours). The short time of the circulation of the drug in blood may be considered inconsistent with the generally recognized time-course of its glucose-lowering effect. Actually, metformin remains in the gastrointestinal tract for a considerably longer time; therefore it may explain the apparent duration of its clinical action. Metformin is predominantly absorbed from the small intestine, with a bioavailability of ~60%. The drug is excreted unchanged in the urine- no metabolites have been identified in humans. As metformin is excreted by the kidneys, creatinine clearance should be measured before initiation of therapy and regularly during treatment [6,8,9]. The main contraindications to metformin therapy are hypersensitivity to metformin or any of the excipients of the preparation, diabetic ketoacidosis, diabetic pre-coma, renal failure or dysfunction (creatinine clearance <60 ml/min), heart failure, respira-

tory failure, recent myocardial infarction, cardiac shock, liver failure, and acute alcohol intoxication. The data concerning the use of metformin in pregnant women are limited but does not indicate an increased risk of congenital malformations. However, when planning pregnancy and during pregnancy, it is recommended not to treat diabetes with metformin, but to use insulin instead. Breastfeeding is also not recommended during metformin therapy because of limited data [6].

Possible causes of gastrointestinal disorders

Despite the very long presence on the pharmaceutical market, a significant number of clinical trials, and a huge number of patients taking this drug, we still know little about the mechanism of metformin adverse effects on the gastrointestinal tract.

Reduced absorption of fatty acids. One of the causes may be the increase of the bile acid pool within the intestine, predominantly through reduced ileal absorption. Reduction in bile acid absorption caused by metformin has been considered a mechanism influencing entero-endocrine function, glucose homeostasis, and lowering cholesterol. The mechanism is based on the inhibition of the bile acid receptor activity, the so-called FXR (Farnesoid X receptor), which re-captures bile acids from the intestinal lumen by a 5'AMP-activated kinase (AMPK). Metformin acts on AMPK, increasing its activity and thus influencing the metabolism of glucose and lipids. However, the increased luminal bile salt concentration may also lead to alterations in the microbiome and cause an osmotic effect (higher fecal bile salt excretion), resulting in diarrhea [1].

Increased synthesis of lactate. The increased concentration of metformin in the intestine, or prolonged exposure of the enterocytes to this drug, increases glucose absorption and its anaerobic metabolism by enterocytes, leading to the rise of plasma lactate concentration (hyperlactatemia). It is believed that both the gut and liver are the primary sources of metformin-related lactate production. Lactate production associated with metformin may result from its action on the gut microbiome by inhibition of glycerophosphate dehydrogenase, found in some gut bacteria. Therefore, it was thought to contribute to the intolerance to metformin, manifested by nausea, vomiting, and abdominal pain [1], [9].

The similarity of the structure of the metformin molecule to serotonin. Serotonin takes part in the stimulation of the peristaltic wave, resulting in the development of diarrhea. Moreover, it activates the serotonin-type 3 receptor (5-HT3) in the chemoreceptor trigger zone (CTZ) area at the floor of the IV ventricle of the brain, which is associated with the development of nausea and vomiting. It has been suggested that metformin competitively binds to the serotonin transporter (SERT), and thus, the concentration of serotonin is increased. A direct serotonergic effect of metformin is also possible, and the drug has been shown to increase serotonin release by enterochromaffin cells in the intestine [1].

Disorders of the intestinal microbiota. The gut microbiota plays a vital role in the regulation of metabolic processes, digestion, absorption and the production of many bioactive particles. The development of intestinal dysbiosis (dissociations between the composition of the gut microbiota and the human host) leads, i.a, to an increase in the concentration of methane, lactates, and inflammatory mediators in the gastrointestinal tract. The dysbiosis of the gut microbiome has been proven to be associated with the development of type 2 diabetes. Furthermore, the implementation of metformin therapy contributes to further changes in the composition of gut microbiota. It has been suggested that metformin affects the composition of gut microbiota through the increase in mucin-degrading bacteria- *Akkermansia muciniphila,* and also several SCFA-producing (short-chain fatty acid) microbiota. In patients treated with metformin, the altered gut microbiota has exerted changes in the gut metabolomics, leading to increased production of butyrate and propionate, involved in glucose homeostasis [10].

Mizerski et al. aimed to compare the incidence of gastrointestinal adverse reactions in patients starting treatment with metformin in the form of fast-release and prolonged-release preparations. About 30 % of patients reported various types of gastrointestinal adverse events, and the proportion of these patients was almost twice as frequent among those taking standard--release metformin. Patients using standard-release metformin most often complained of decreased appetite (10.28%), abdominal pain and nausea (9.71% each), and a metallic taste in the mouth (8.57%). Flatulence (4.57%) and diarrhea (4%) were less frequent. On the other hand, among people using the extended-release metformin, the most common symptoms were flatulence (12.5%) and diarrhea (11.45%), both of which were significantly more common in patients taking prolon-

ged-release tablets (SR- slow release) compared to the immediate release (IR) form (p = 0.0169, p = 0.0185, respectively). Other complaints were significantly less frequent among patients who took the prolonged-release drug [3]. McCreight et al. performed an open-label pharmacokinetic study to investigate the hypothesized mechanisms and assess potential causes of metformin intolerance. They studied the differences between the individuals tolerant to metformin (10 participants) and those who are intolerant (10 participants) by measuring metformin and serum lactate concentrations, along with targeted metabolomics, in the hours following the administration of a single dose of metformin 500 mg (IR). No significant difference was identified between tolerant and intolerant cohorts in metformin pharmacokinetics, systemic measures of lactate, serotonin or bile acids. This may suggest that metformin intolerance in these patients may be related to local factors within the lumen or enterocyte; however, further studies on a larger number of participants would be advisable [9].

Conclusion

Metformin, which has been effectively applied in patients with type 2 diabetes for decades, exerts beneficial effects on lowering blood glucose levels and weight control. However, the therapy with this substance may entail the risk of adverse reactions. The intolerance to metformin most commonly manifests itself as gastrointestinal disorders, such as nausea, vomiting, diarrhea, abdominal pain and loss of appetite, which resolve spontaneously in most cases. The most probable mechanisms responsible for intolerance to metformin and the above-mentioned ailments are abnormal uptake, increased lactate production, accumulation of serotonin, histamine or bile acids and gut microbiota dysbiosis. These adverse reactions pose a therapeutic challenge because of their ambiguous character. It highlights the importance of informing the patient at the beginning of metformin therapy about all the treatment aspects. In the event of gastrointestinal problems, one should not discontinue the drug, but reduce the dose and then try to increase it slowly as it may improve the drug's gastrointestinal tolerance.

Conflict of interest
None

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