

The influence of comorbidities on complications of warfarin therapy among geriatric patients – a case report of a 77-year-old patient with scrotal hernia

Wpływ chorób współistniejących na powikłania terapii warfaryną wśród pacjentów geriatrycznych – opis przypadku 77-letniego pacjenta z przepukliną moszną

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Abstract

The case report concerns a 77-year-old man with hematuria caused by warfarin overdose. The patient was also found to have a scrotal hernia containing a large part of the intestines in the hernial sac, which may have impaired the intestinal absorption of warfarin, reduced its binding to plasma proteins, and consequently led to an overdose of the drug. The aim of the study is to draw attention to the difficulties in the treatment of vitamin K antagonists in the elderly, which requires special care. This is due to changes in warfarin metabolism, so they should be given lower doses compared to younger patients. The described case also reminds us how important it is to pay attention to the pharmacodynamics and pharmacokinetics of active substances that may change as a result of diseases that interfere with the absorption of drugs, e.g. hernia. Laboratory tests showed a significant increase in the INR level to 23.2, high parameters of inflammation and normocytic anemia. Physical examination and imaging revealed a massive bilateral scrotal hernia. After discontinuation of warfarin, the hematuria resolved and the INR level normalized. Warfarin is an anticoagulant that is still widely used, especially in patients with atrial fibrillation. However, treatment of an elderly patient burdened with multiple diseases and at risk of polypharmacy should be particularly careful in order to minimize the risk of bleeding. It is necessary to monitor the INR frequently and educate the patient about the need to take appropriate doses of the preparation on a regular basis. Other diseases, including surgical ones, can affect the metabolism of drugs, so it is important to carefully examine the patient each time. In each case, the thromboembolic risk and the risk of bleeding should be assessed and the therapy with the greatest benefit and the lowest risk of complications determined. (Gerontol Pol 2023; 31; 288-294) doi: 10.53139/GP.20233128

Keywords: warfarin, scrotal hernia, pharmacokinetics, elderly patients, multimorbidity

Streszczenie

Opis przypadku dotyczy 77-letniego mężczyzny, u którego wystąpił krwiomocz spowodowany przedawkowaniem warfaryny. U pacjenta stwierdzono również przepuklinę moszną, zawierającą znaczną część jelit, co mogło spowodować zaburzenie jelitowego wchłaniania warfaryny, ograniczenie jej wiązania z białkami osocza, a w konsekwencji doprowadzić do przedawkowania leku. Celem pracy jest zwrócenie uwagi na trudności w leczeniu antagonistami witaminy K u osób starszych, które wymaga zachowania szczególnej ostrożności. Wynika to ze zmian metabolizmu warfaryny, dlatego należy podawać im mniejsze dawki w porównaniu z młodszymi pacjentami. Opisany przypadek przypomina jak ważne jest zwrócenie uwagi na farmakodynamikę i farmakokinetykę substancji czynnych, które mogą ulec zmianie w wyniku schorzeń zaburzających wchłanianie leków, np. przepukliny. W badaniach laboratoryjnych stwierdzono znaczne podwyższenie poziomu INR do wartości 23.2, wysokie parametry stanu zapalnego oraz niedokrwistość normocytarną. W badaniach przedmiotowych i obrazowych stwierdzono maszyną obustronną przepuklinę moszną. Po odstawieniu warfaryny krwiomocz ustąpił, a poziom INR uległ normalizacji. Pacjentowi zaproponowano zmianę leczenia na lek z grupy NOAC, lecz chory odmówił ze względów ekonomicznych. Warfaryna to antykoagulant, który jest wciąż szeroko stosowany, zwłaszcza u pacjentów z migotaniem przedsionków. Prowadzenie terapii chorego w podeszłym wieku, obciążonego wielochorobowością i narażonego na zjawisko polipragmazji, powinno być jednak szczególnie ostrożne, aby zminimalizować ryzyko krwawienia. Niezbędne jest częste monitorowanie INR oraz edukacja pacjenta o konieczności regularnego przyjmowania odpo-

wiednich dawek preparatu. Inne schorzenia, w tym chirurgiczne, mogą wpływać na metabolizm leków, dlatego ważne jest każdorazowe dokładne zbadanie pacjenta. W każdym przypadku należy oszacować ryzyko zakrzepowo-zatorowe, ryzyko krwawień oraz ustalić terapię niosącą najwięcej korzyści przy najmniejszym ryzyku powikłań. (*Gerontol Pol* 2023; 31; 288-294) doi: 10.53139/GP.20233128

Słowa kluczowe: warfaryna, przepuklina mosznowa, farmakokinetyka, pacjenci w podeszłym wieku, wielochorobowość

Introduction

According to statistics, it is estimated that around 6 million Europeans suffer from atrial fibrillation (AF). This disease is responsible for 20% of ischemic strokes, therefore, in the described group of patients, in the absence of contraindications, it is necessary to use antithrombotic prophylaxis. Despite the introduction of drugs from the group of New Oral Anticoagulants (NOACs), warfarin still occupies an important place in the therapy of patients with atrial fibrillation, belonging to vitamin K antagonists, which the world of medicine heard about as early as the 1940s. Therapeutic doses of this drug reduce the total amount of each of the vitamin K-dependent coagulation factors by 30-50%, thereby reducing the risk of thromboembolism in the course of atrial fibrillation. However, the side effects of warfarin use should be borne in mind, including, above all, the increased probability of bleeding, especially in elderly patients with multimorbidity and polypharmacy [1,2].

This paper describes the case of a geriatric patient with hematuria caused by warfarin overdose. The patient was also found to suffer from scrotal hernia containing a large part of the intestines, which may have impaired the intestinal absorption of warfarin, reduced its binding to plasma proteins, and consequently led to an overdose of the drug and achieved significantly elevated INR values.

The aim of the study is to draw attention to the difficulties in the treatment of vitamin K antagonists in the elderly, which requires special care. This is due to changes in warfarin metabolism, so they should be given lower doses compared to younger patients. The described case reminds us how important it is to know the pharmacodynamics and pharmacokinetics of active substances that may change as a result of diseases that interfere with the absorption of drugs, e.g. hernia.

A case report

A case report concerns a 77-year-old man with hematuria resulting from coagulation disorders caused by an overdose of warfarin (INR 15.73). Physical examination revealed a grade IV pressure ulcer in the sacral area and bilateral inguinal hernia. During hospitalization, the patient was also diagnosed with a urinary tract infection

and a scrotal hernia containing a large part of the intestines, which did not show signs of incarceration. In the patient's medical history, there were also: prostate cancer after the completion of oncological treatment and a history of post-radiation proctitis. The man is chronically ill with: Parkinson's disease, arterial hypertension of unknown duration, secondary myocardial pathology with paroxysmal atrial fibrillation, chronic gastritis, sigmoid diverticulosis, polyarthritis and left kidney cyst. In 2017, the patient underwent colon polyps removal. Recently, he also suffered a fracture of the right ribs and an infection of the gastrointestinal tract caused by *C. difficile*. A month earlier, the patient had been hospitalized, also due to a warfarin overdose. The INR level at that time was 23.32.

Diagnostic process

The patient underwent laboratory blood tests, which showed elevated signs of inflammation (CRP 153.08) and normocytic anemia (RBC 3.58, HGB 9.7 and HCT 29.8). In addition, decreased calcium levels, vitamin D3 deficiency, hypoalbuminemia and hyponatremia were demonstrated. Due to the presence of hematuria, the parameters of the coagulation system were regularly determined, which showed significant abnormalities in the form of their prolongation: APTT (105.8), PT (182.8), prothrombin index (6.1) and INR (15.73). Due to the bleeding, the state of the iron economy was examined. The patient showed decreased iron (15.3), transferrin (0.8) and elevated ferritin level (382). The results of the general urine test showed the features of UTI (blood urine, cloudy urine, presence of protein in the urine 238.8 mg/dl and numerous bacteria, leukocytes, erythrocytes and calcium oxalate crystals). Due to high parameters of inflammation, urine and blood cultures were performed, which showed the presence of *P. aeruginosa* and *E. faecium*. Due to the patient passing loose stools, a stool test for *C. difficile* was performed with a positive result. Due to concomitant heart failure, an ECG was performed and there were isolated supraventricular extrasystoles. No atrial fibrillation was recorded during the examination. A chest X-ray was also performed, which showed opacity of the left phrenic-costal angle, fluid in the left pleural cavity and small densities that may suggest atelectasis.

Due to the presence of bilateral scrotal hernia, the patient was referred for a surgical consultation. Due to the high risk of postoperative complications and the expected dubious improvement in the patient's quality of life after a possible surgery, and the lack of absolute indications, i.e. incarceration or intestinal ischemia, the procedure was abandoned. Continuation of the current treatment was recommended, with particular emphasis on anti-bedsores prophylaxis. During hospitalization, a Foley 20F catheter was inserted and a urine culture was taken.

Differential diagnosis

The patient was diagnosed with two warfarin overdoses based on too high INR values. The differential diagnosis should take into account deficiencies of coagulation factors, especially those dependent on vitamin K, i.e. II, V, VII and X, as well as fibrinogen deficiencies and dysfibrinogenemia. However, these are hereditary diseases and very rare. They may be manifested by skin changes in the form of petechiae or bleeding, but a significant part may also be asymptomatic or oligosymptomatic [3].

Vitamin K is needed for the formation of coagulation factors. Its deficiency can also lead to prolonged prothrombin time and INR. It can occur e.g. as a result of low dietary intake, liver diseases, impaired absorption in the gastrointestinal tract or the use of certain drugs, e.g. vitamin K antagonists [4].

The place of production of coagulation factors is the liver, therefore acute or chronic damage to its parenchyma should also be taken into account. Improper functioning of this organ also leads to disorders of homeostasis [5]. In the case of disseminated intravascular coagulation (DIC), there is systemic activation of coagulation processes. At the same time, blood clots form in the microcirculation and symptoms of hemorrhagic diathesis appear due to increased consumption of coagulation factors, platelets and fibrinogen. DIC can be acute, e.g. in sepsis, or chronic, e.g. in malignant tumors [6]. Vitamin K antagonists are coumarin derivatives. These compounds can also be found, for example, in rodenticides, the consumption of which can lead to poisoning, which should also be taken into account in the course of differential diagnosis.

Applied treatment

During the first hospitalization due to a high INR resulting from an overdose of warfarin, this drug was discontinued and treatment with vitamin K preparations was introduced, leading to the normalization of the aforementioned index. Withdrawal of the anticoagulant would not be sufficient in this case, as the INR has reached 23.32, and at an INR >6 it does not stabilize within 24 hours. In this situation, it was necessary to administer additional vitamin K orally [7]. After the INR was corrected, a pressure ulcer was surgically debrided on the sacrum. It was proposed to change the anticoagulant to NOAC, but the patient did not agree, justifying his decision on economic grounds. During the second hospitalization for hematuria, in addition to discontinuation of warfarin, cyclonamin and tranexamic acid were administered, which were discontinued after resolution of hematuria. Due to the low level of hemoglobin, two units of RBC were transfused. Rivaroxaban was temporarily introduced, but due to bleeding from the pressure ulcer, the CHA₂DS₂-VASc and HAS-BLED scales were assessed and anticoagulant treatment was discontinued. Both relate to the assessment of patients with atrial fibrillation. The first is used to estimate the risk of ischemic stroke, the second is used to assess the risk of bleeding in these patients. Due to high parameters of inflammation reflecting UTI and *C. difficile* infection, the patient was started antibiotic therapy including ceftriaxone and vancomycin. According to the guidelines, for the first infection caused by *Clostridioides difficile*, it is recommended to administer vancomycin four times a day at a dose of 125 mg, which was used in the case of the patient [8].

Recommendations

During hospitalization, the patient's condition improved and he was transported home in a good general condition. Further recommendations were developed and presented to both the patient and his wife. They focused on further treatment of the coccyx bedsores, periodic replacement of the urinary catheter, performing control tests of the complete blood count, ionogram and coagulation times as well as proper nutrition and hydration of the patient, and regular medication, including iron supplementation, due to the diagnosed anemia associated with deficiency of this element.

The most important in the case of the described patient seem to be decisions related to further anticoagulant treatment. During his stay at the Geriatrics Ward, the patient was assessed for thromboembolic risk, obtaining 3

points on the CHA₂DS₂-VASc scale (2 points for age over 75), which qualified him to the high risk group of ischemic stroke, but at the same time the patient was assessed for bleeding risk on the HAS-BLED scale, also scoring 3, which also meant that the patient was at high risk.

Guided by the latest scientific reports and trying to select the appropriate treatment for the described patient, it was decided to propose a change of the current therapy using warfarin to one based on NOAC. However, the patient and his caregivers, after learning about the current costs of the presented drugs, did not agree to change the treatment, arguing the decision for economic reasons. During the first hospitalization, the described patient was recommended to continue the therapy with the use of warfarin, subject to the required regular INR control within the Primary Health Care. However, after returning to the hospital for a second overdose, after re-evaluating the thromboembolic and haemorrhage risks, and considering the need for two hospitalizations for a warfarin overdose in rapid succession, it was decided to discontinue anticoagulant therapy. During hospitalization, ECG examinations showed sinus rhythm in the patient each time, which also determined the resignation from warfarin therapy. Due to the decision not to continue the pharmacotherapy, the patient was considered to undergo surgery to close the left atrial appendage in order to prevent thromboembolic events, i.e. ischemic stroke. This action is indicated in the case of patients with atrial fibrillation in whom there are contraindications to the long-term use of anticoagulants. In the described case, however, it was finally decided not to perform the procedure due to the high risk of perioperative complications.

Mechanism of action and principles of warfarin use

Warfarin is a drug belonging to the group of vitamin K antagonists (VKAs) and, as the name suggests, its main mechanism of action is the inhibition of the physiological effects of substances whose synthesis depends on the aforementioned vitamin. We are talking here primarily about coagulation factors II, VII, IX and X, for which it is a cofactor, the role of which is based on the post-translational carboxylation of glutamic acid residues present in their structure to γ -carboxyglutamic acid. Without this process, it prevents the coagulation factors from combining with calcium cations, and thus it is impossible for them to bind to phospholipids on the surface of the membrane and be transported from the liver to the circulating blood, where they could take part in coagulation processes. As already mentioned, the presence of

the appropriate form of vitamin K - reduced hydroquinone - is essential for the occurrence of these reactions. During the process, it is oxidized to epoxide, and then reduced again with the help of vitamin K epoxide reductase (VKOR), thanks to which the cycle closes and the activation of other coagulation factors can start again. The action of warfarin is based on the inhibition of the VKOR enzyme and the processes dependent on it, and thus preventing the restoration of the reduced form of vitamin K. Thus, the described group of drugs has anticoagulant activity, and their effect can be reversed by vitamin K supplementation [9].

Warfarin, like other drugs from the group of vitamin K antagonists (VKAs), is well absorbed from the gastrointestinal tract after oral administration. It has an elimination half-life of approximately 40 hours, which corresponds to a moderately long duration of action. It is characterized by high affinity (99%) to plasma proteins, with which it forms protein-drug complexes. This prevents warfarin from being displaced from these conjugates by competitive inhibition mechanisms that often occur in the body due to the simultaneous use of several drugs with affinity for the same plasma proteins. Warfarin is metabolised in the liver by highly polymorphic CYP2C9, therefore it may be less metabolized in patients with genetically reduced activity of this cytochrome isoform. This necessitates dose adjustments, usually by reducing doses, to prevent bleeding events. In the course of metabolic processes, warfarin undergoes significant biotransformation, including i.a. hydroxylation, conjugation with glucuronic and sulfuric acid. Finally, in the form of products of these reactions, it is excreted in the urine by the kidneys. The metabolism of this substance is affected by some other drugs that may interact with it. Pharmaceuticals that may displace warfarin from binding to proteins and inhibit its biotransformation, thus increasing the risk of bleeding, include, among others: sulfonamides, allopurinol, non-steroidal anti-inflammatory drugs (NSAIDs), chloramphenicol, proton pump inhibitors (PPIs) or tolbutamide. Other substances, i.e. quinidine, tetracyclines or salicylates, may cause similar effects through a synergistic effect in relation to the vitamin K antagonist. It should also be noted that the simultaneous use of warfarin and cholestyramine reduces the degree of VKA absorption from the gastrointestinal tract, weakening its anticoagulant effect [10].

Since 1983, the reference method recommended by the World Health Organization for monitoring the patient's condition during warfarin therapy is the determination of the prothrombin index raised to the power of the ISI (international sensitivity index) - INR. The dose of the described drug must be individually selected for

each patient, due to individual variability and the effect of action, which is difficult to predict. For this purpose, for the first 5-7 days after the introduction of treatment, strict monitoring of the INR is carried out, but it should be remembered that its decrease below 2 increases the thromboembolic risk, while reaching a value greater than 4.5 increases the risk of bleeding, which may be a complication therapy with vitamin K antagonists. Once the appropriate dose is found, warfarin should be taken by the patient at the same time each day. In Poland, it is registered for use in the treatment and prevention of deep vein thrombosis and pulmonary embolism, secondary prevention of myocardial infarction, prevention of thromboembolic complications (stroke or embolism in the peripheral circulation) after a heart attack, prevention of thromboembolic complications (stroke or embolism in the peripheral circulation) in peripheral circulation) in patients with atrial fibrillation, with valvular pathology or after prosthetic valves [11].

Discussion

According to the American Association of Poison Control Centers data from 2014, 1,766 cases of warfarin overdose were registered in the USA during the year. Of these, 84% involved an unknowing drug overdose. During this time, 16 cases requiring medical attention were reported, but none of them resulted in the patient's death. Geriatric patients are more exposed to the effects of warfarin overdose, both due to age-related changes in the body affecting metabolism, which may intensify the effect of the drug, and cognitive problems, increasing the risk of its incorrect administration, inconsistent with the recommended dosage [12].

So far, the described patient used warfarin-based therapy, which is characterized by many side effects and, due to the high risk of bleeding complications, requires strict therapeutic adherence and patient cooperation. This may be limited by the patient's advanced age, male gender, the need for long-term treatment, mental illnesses, dementia, low education, high drug costs, lack of knowledge about one's condition, fear of side effects of therapy, lack of support from loved ones, reduced motivation and loneliness. In the case of the patient described in this paper, many of these factors were met, which confirms the repeatability of hospitalization due to warfarin overdose and significantly elevated INR. The presence of a massive scrotal hernia containing the intestines could also adversely affect the metabolism of warfarin by interfering with the pharmacokinetics of the drug [13].

As a standard, anticoagulant therapy is recommended for all patients who score 3 or more on the CHA₂DS₂-VASc scale. However, this applies only to patients who have no contraindications to the above-mentioned therapy. Its main limitation is the increased risk of serious bleeding complications, which is assessed using the HAS-BLED scale. Patients taking drugs that reduce blood coagulability require elimination of reversible risk factors, i.e. uncontrolled hypertension, labile INR values during VKA therapy, simultaneous use of preparations containing substances that increase the risk of bleeding (e.g. acetylsalicylic acid, non-steroidal anti-inflammatory drugs) and alcohol [14]. According to the current guidelines of the European Society of Cardiology, the presence of bleeding risk factors is not an absolute contraindication to the use of anticoagulant prophylaxis in patients with atrial fibrillation, however, efforts should be made to limit and eliminate the above-mentioned reversible potential causes of bleeding, which turned out to be too difficult in the case of the patient described in this article. In addition, during hospitalization the patient presented sinus rhythm, which excludes the diagnosis of persistent atrial fibrillation. In subclinical forms of the described disease, it is recommended to assess the appropriateness of anticoagulant treatment each time on the basis of the patient's current condition, thromboembolic risk factors as well as the duration and load of atrial fibrillation [15].

In recent years, drugs from the NOAC group have become very popular and have been used interchangeably with warfarin, also in patients with atrial fibrillation. In a study by Rutherford et al. in elderly patients with AF at high risk of thromboembolic complications, the use of standard doses of NOACs was found to be as effective in preventing ischemic events as warfarin with a reduced or comparable risk of complications hemorrhagic [16]. However, in the case presented in this paper, the patient refused to switch to NOAC for economic reasons. This proves how big a problem in the comprehensive treatment of patients can be its costs and reimbursement limitations [17]. So far, in Poland, NOAC drugs are not reimbursed for patients with atrial fibrillation requiring thromboprophylaxis.

Conclusions

This paper presents data that highlight the still widespread use of vitamin K antagonists for the prevention of thromboembolic events. Despite the availability of more modern and possibly safer generations of drugs, warfarin remains a popular choice, especially in patients with atrial fibrillation. Justification can be sought in economic

factors. The low price of the described drug is a great advantage for patients requiring chronic treatment. However, during the therapy of the elderly, the focus should be on maximizing the individualization of therapy and holistic treatment of the patient.

Other diseases, including surgical ones, may affect the metabolism of drugs, therefore it is important to carefully examine the patient each time and assess the thromboembolic risk, the risk of bleeding, and determine the therapy that brings the most benefits with the lowest risk of complications. Under normal conditions, warfarin preparations, after oral administration, are digested in subsequent sections of the gastrointestinal tract, after which the active substance is absorbed into the peripheral blood within the small intestine. If a patient develops a hernia containing intestinal loops, the possible consequences of this condition, resulting from the influence on the metabolism of the anticoagulant, should be taken into account. The section of the intestine covered by the hernial sac shows a reduced ability to absorb substances present in the digestive tract, both as a result of peristalsis disorders and impaired tissue blood supply. In some cases, incarceration of the hernia may also occur, as a consequence of which the hernia gates tighten on the intestinal loops contained in the peritoneal sac, causing their significant ischemia and even complete obstruction or strangulation leading to tissue necrosis. The consequence of these phenomena is a decrease in the ability to absorb warfarin into the blood. In addition, within the hernial sac of the intestine, there are products of the initial metabolism of the drug, which, despite impaired absorption, pass through the intestinal-blood barrier. This leads to an increase in the concentration of potentially toxic metabolites of the drug in the peripheral blood, and thus to the possibility of symptoms resulting from an unintentional overdose of warfarin. It follows that when

planning anticoagulant therapy in each patient with a diagnosed hernia, the possible influence of this disease on the pharmacokinetic and pharmacodynamic processes of the drug should be considered. In the case of suspicion of a so far undiagnosed hernia, it is worth consulting the patient with a surgeon and performing imaging tests, i.e. ultrasound, in order to assess its contents.

Due to many comorbidities and high risk of adverse effects of polypharmacy, geriatric patients are a group of patients in whom the use of anticoagulants may be particularly dangerous. It is always necessary to make sure that a given senior does not use other substances that may affect the metabolism and potency of warfarin on a chronic basis, and to educate him and any caregivers about the need to follow the recommendations. Effective cooperation with the patient and his family is extremely important, which, unfortunately, in the case of elderly people may be difficult, among others, due to the increased incidence of dementia and cognitive disorders and all kinds of disabilities in this group of patients. The regularity of taking medications and appearing for check-ups to monitor test results and the course of therapy may be disturbed. It is necessary to increase the vigilance of the attending physician and family medicine specialists, whose task should be to make every effort to provide the patient with the highest possible safety profile of the therapy used. If warfarin-based therapy is introduced, frequent monitoring of the INR and reporting of any adverse effects observed by the patient or their caregivers should be recommended. Both thromboembolic and bleeding risk should be systematically assessed and, if necessary, vitamin K antagonist therapy should be modified or discontinued if contraindications occur.

Conflict of interest

None

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