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CASE REPORT

THE DILEMMA OF ANTICOAGULANT THERAPY IN A PATIENT WITH MECHANICAL AORTIC VALVE AND UNSTABLE INR LEVELS TO PREVENT SECONDARY STROKE – A CASE STUDY

DYLEMAT LECZENIA PRZECIWZAKRZEPOWEGO U PACJENTA Z MECHANICZNĄ ZASTAWKĄ AORTALNĄ I NIESTABILNYMI WARTOŚCIAMI INR W ZAPOBIEGANIU WTÓRNEMU UDAROWI MÓZGU – STUDIUM PRZYPADKU

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ABSTRACT

Historically, in high-risk patients with cardiovascular disease, anticoagulants have been used in order to reduce the risk of stroke or other ischemic complications. However, despite this seemingly simple solution, drug selection and dosage control may provide a unique challenge when it comes to the anticoagulation therapy of individual patients. In this case report, a patient with multiple underlying conditions and two previous stroke episodes was admitted due to decompensated heart failure and was treated with anticoagulants to reduce the risk of developing secondary stroke(s). The initially prescribed anticoagulative agent, acenocoumarol, was discontinued and subsequently replaced with enoxaparin due to unstable INR and undiagnosed anaemia. Unfortunately, newer anticoagulants were contraindicated in this patient due to the previous implantation of the mechanical aortic valve. This study reveals and discusses the conundrum faced in prescribing anticoagulants to patients with multiple conditions of underlying diseases. Despite the aforementioned hurdles, anticoagulant therapy in these patients is crucial in avoiding potential life-threatening complications, including myocardial infarction and secondary stroke; proper prescription decisions may ultimately decrease morbidity and improve the quality of life of these high-risk patients.

Keywords: secondary stroke, stroke prevention, cardioembolism, anticoagulation therapy

STRESZCZENIE

Historycznie, u pacjentów wysokiego ryzyka z chorobami układu krążenia, antykoagulanty stosowano w celu zmniejszenia ryzyka udaru lub innych powikłań niedokrwiennych. Jednak pomimo tego pozornie prostego rozwiązania, dobór leków i kontrola dawkowania może stanowić wyjątkowe wyzwanie w terapii przeciwkrzepliwej poszczególnych pacjentów. W niniejszym opisie przypadku pacjent z wieloma chorobami podstawowymi i dwoma poprzednimi epizodami udaru mózgu został przyjęty z powodu niewyrównanej niewydolności serca i był leczony lekami przeciwzakrzepowymi w celu zmniejszenia ryzyka wystąpienia wtórnego udaru mózgu. Początkowo przepisany lek przeciwzakrzepowy, acenokumarol, został odstawiony, a następnie zastąpiony enoksaparyną ze względu na niestabilny INR i niezdiagnozowaną anemię. Niestety nowsze antykoagulanty były przeciwwskazane u tego pacjenta ze względu na wcześniejszą implantację mechanicznej zastawki aortalnej. Niniejsze badanie ujawnia

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i omawia zagadkę, z jaką należy przepisywać leki przeciwzakrzepowe pacjentom z wieloma schorzeniami leżącymi u podstaw chorób. Pomimo wspomnianych przeszkód, leczenie przeciwzakrzepowe u tych pacjentów ma kluczowe znaczenie dla uniknięcia potencjalnych powikłań zagrażających życiu, w tym zawału mięśnia sercowego i wtórnego udaru mózgu; właściwe decyzje dotyczące przepisywania leków mogą ostatecznie zmniejszyć zachorowalność i poprawić jakość życia tych pacjentów wysokiego ryzyka.

Słowa kluczowe: wtórny udar wtórny, profilaktyka udaru, zator sercowo-naczyniowy, terapia przeciwzakrzepowa

Introduction

The association between ischemic stroke and the clotting of blood in cerebral arteries is well-documented in medical academia; it is understood that these clots may originate as a result of various cardiovascular conditions, including atrial fibrillation, valvular diseases and contractility dysfunction due to long-lasting hypertension. In patients who have a medical history of cardiovascular and valvular diseases, anticoagulants are used in order to reduce the risk of complications, including strokes. However, despite this seemingly straightforward solution, drug selection and dosage control may provide a unique challenge when it comes to the anticoagulation therapy of individual patients with conditions of underlying diseases. Anticoagulants are used to treat a number of cardiovascular diseases. Atrial fibrillation, stroke prevention, postoperative regimen, and prosthetic valve implantation are common indications for anticoagulation therapy. Warfarin and heparin are traditional anticoagulants, where monitoring of international normalized ratio (INR) and activated partial thromboplastin time (aPTT) are respectively required. Heparin is often used merely in hospital settings, as it could only be administered by intravenous (i.v.) or subcutaneous (s.c.) injection. Moreover, patients taking warfarin or other vitamin K antagonist (VKA) should strictly follow a restricted diet. They should always avoid eating foods that consist high amount of vitamin K, such as green leafy vegetables. Alcohol consumption could also affect the effectiveness of warfarin. Therefore, drinking alcohol is not recommended in these patients. Medications, particularly some antibiotics including macrolides, should always be prescribed with caution in patients taking warfarin due to potential drug interactions. The novel oral anticoagulants (NOACs) include dabigatran (direct thrombin inhibitor), apixaban, rivaroxaban, and edoxaban (all three are factor Xa inhibitors). They are more patient-friendly due to the proper route of administration, while monitoring is not required. However, unlike the traditional anticoagulants, there are limited antidotes for overdoses, with the exception of idarucizumab for dabigatran. Besides, the price of NOACs is relatively higher than traditional anticoagulants, which could be a great disadvantage for some groups of patients, especially when anticoagulative therapy is often life-long management as the preferences of the patients are also important for compliance. The choice of prescribed anticoagulants is dependent on the patient's individual condition, and the guideline indications of different anticoagulants are summarized in Table 1 (Otto *et al.*, 2021; Unger, 2019).

Case

Admission: patient description and physical examination

A 70-year-old male with a history of two strokes and myocardial infarction was admitted to the emergency department and then referred to the cardiology ward on the 25th of March 2021 due to the symptoms of chronic heart failure exacerbation. The patient complained about increasing fatigue,

exertional dyspnoea and increasing abdominal girth with accompanying pain. He notified the admitting physician about gaining 10 kg within 4 weeks. In clinical examination, symmetrical crackles were heard below inferior angles of the scapulas, indicating basal pulmonary congestion. Aside from pulmonary oedema, severe peripheral oedema reaching up to the patient's scrotum and ascites were present. The fluid retention was more pronounced at the left side, possibly as a result of post-stroke hemiparesis. An ejection click sound with accompanying systolic flow murmur was heard at the aortic valve during auscultation of the heart. Slurred speech and delayed response were observed during the examination.

Case history

The patient suffers from a wide range of underlying conditions including dilated cardiomyopathy with heart failure (ejection fraction of 24%), previous myocardial infarction, hypertension, impaired fasting glycaemia, hyperuricemia, hyperlipidaemia, episode of ischemic stroke and subarachnoid haemorrhage, aneurysm of the ascending aorta (88 mm), benign prostate hypertrophy (BPH), chronic kidney disease, iron deficiency anaemia and rectal adenocarcinoma G1. The patient is also allergic to penicillin.

Because of severe mixed aortic valve disease (coexistence of aortic stenosis and aortic regurgitation), the patient has had a prosthetic aortic valve since 1989. Simultaneously he underwent implantation of ventricular demand pacing (VVI) pacemaker due to a third-degree atrioventricular block. The VVI pacemaker was then replaced by a dual-chamber anti-bradycardia (DDD) pacemaker in 2006 and a new version in 2014. The DDD pacemaker was recently replaced by a cardiac resynchronization therapy defibrillator (CRT-D) pacemaker in 2019.

In 2000, the first stroke occurred in the right hemisphere of the brain. The Computer Tomography (CT) scan revealed an ischemic stroke with no signs of hemorrhage. According to the Oxfordshire Community Stroke Project (OCSP) classification system, this is believed to be partial anterior circulation syndrome that commonly involves the occlusion of middle cerebral arteries (Bamford *et al.*, 1991). The stroke caused permanent impairment of the left side of the body with classic clinical features including left-sided weakness and slurred speech. The second stroke happened in 2007 due to a spontaneous subarachnoid hemorrhage. The incidents of the stroke are suspected to be related to cardiac events.

In 2017, the patient had an ST-elevated myocardial infarction (STEMI) due to the occlusion of the left anterior descending (LAD) coronary artery. The cardiologist attempted to insert a stent during the percutaneous coronary intervention (PCI) but did not succeed due to anatomical reasonings. Conservative therapy was provided to slow down the progression of coronary artery disease and to prevent worsening of symptoms.

Aneurysm of the ascending aorta was diagnosed in 2019, and it was treated merely with a non-selective beta-blocker, carvedilol, to control the blood pressure strictly as the patient was not suitable for operation.

The intestinal adenocarcinoma G1, which probably caused the anemic condition of the patient, was surgically removed utilizing endoscopic resection recently on the 1st of March 2021.

Family medical history revealed that the patient's mother suffered from a stroke when she was 70, and her father experienced myocardial infarction.

The patient also claimed that he used to be a heavy smoker, 20 cigarettes per day, currently reduced to 4 cigarettes per day. He consumes alcohol occasionally, once or twice per week.

Results of pathological tests and other investigations

Laboratory examination revealed a slightly increased C-reactive protein (CRP) of 12.6 mg/L on admission and later raised to 33.8 mg/L suggesting inflammation development.

The NT-proBNP was 2309 pg/mL, which was approximately 18 times higher than average. Troponin T was also increased to 38 ng/l on admission and was elevated to 50 ng/l when measured two days post-admission. The INR appeared to be fluctuating and elevated as high as 4.94 (normal range 0.86–1.14). For patients with prescribed VKA because of the mechanical aortic valve and coexisting additional risk factors, the INR should be maintained at 2.5 (range 2.0–3.0). The patient's complete blood count morphology (CBC) also indicated microcytic anemia (MCV < 80 fl). Other laboratory findings include borderline hyponatremia, possibly as a result of fluid accumulation, elevated creatinine level, and a GFR of < 60 mL/min, which indicates chronic kidney disease in stage G3a. The results of the laboratory examination can be found in Table 2.

Echocardiography was performed, and the ejection fraction was 24% indicating severe heart failure. Widening of the QRS complex and ventricular pacing with the regular rhythm of 70 bpm were observed in the resting ECG, suggesting that the pacemaker was working properly.

Medication

- acenocoumarol switched recently to enoxaparin due to unstable INR levels
- carvedilol
- ramipril
- spironolactone & furosemide
- omeprazole
- allopurinol
- potassium supplement
- tamsulosin
- atorvastatin
- iron supplement

Discussion

Challenges in prescribing anticoagulants

The underlying conditions in this patient made the prescription of anticoagulant agents difficult. Despite the difficulties, anticoagulant therapy in this patient is essential due to several reasons and to reduce the risk of secondary stroke. The patient previously experienced two episodes of stroke, one in 2000 and the second one in 2007.

A CT scan was performed in 2000 after obvious clinical features of the right hemisphere stroke were observed. There was no haemorrhage observed in the CT which suggested an ischemic stroke. Most commonly, partial anterior circulation stroke syndrome (PACS) could occur where the middle cerebral artery was obstructed. The second stroke in 2007 stemmed from spontaneous subarachnoid hemorrhage. The two strokes are suspected to be related to the cardiac events, as the patient has a mechanical aortic valve and an implanted pacemaker due to third-degree atrioventricular block in 1989. Lifelong anticoagulant therapy was required to avoid serious complications, including secondary stroke. The patient was started on warfarin.

The patient experienced a STEMI in 2017, and a PCI was performed. However, stents could not be inserted due to anatomical reasons. Carvedilol and statins were prescribed as a long-term post-MI treatment. The numerous cardiac events and the post-stroke experiences put the patient at great risk of having a secondary stroke. Since the patient needs life-long anticoagulation medications, new anticoagulant agents such as rivaroxaban could possibly improve his quality of life. Routine monitoring of INR is not required for this class of medication, and it could be conveniently administered orally. However, NOACs are yet to be approved in patients with artificial valves due to insufficient studies and clinical trials supporting the safety and effectiveness of such patients. A previous study comparing warfarin to dabigatran in patients with prosthetic valves was prematurely terminated due to undesirable events, including excess thromboembolic and hemorrhagic events, observed in the dabigatran group. The study concluded that replacing warfarin with dabigatran in patients with prosthetic valves not merely shows no benefits clinically but also increase the risk of adverse effects such as bleeding complications. (Eikelboom *et al.*, 2013)

In this situation, only the two types of medication, vitamin K antagonists (acenocoumarol or warfarin) and heparin, are suitable for this patient. Acenocoumarol was initially prescribed but switched by the family doctor to enoxaparin in February 2021 due to an unstably high INR. The fluctuations of INR level could be associated with an increased risk of bleeding complications in patients with mechanical valves. Additionally, the patient presented with undiagnosed anemia, which could presumably be associated with gastrointestinal bleeding due to colorectal cancer or its recent surgical removal. Warfarin is relatively unsafe in patients who have a positive history of subarachnoid hemorrhage. Due to anemia, potential postoperative bleeding, and INR issues prescribing warfarin was not a favourable option. During the admission, the patient was receiving heparin as an anticoagulant. However, heparin is only available as a parenteral form, and bluish-colored skin was already observed at the spot of injection. After the hospital discharge, the patient was re-educated about maintaining a strict INR control in cooperation with his family physician, and warfarin was then tentatively prescribed.

According to the bleeding risk index, each point is assigned to the following bleeding risk factors with a maximum of 4 points: age > 65 years, history of stroke, history of gastrointestinal bleeding, and a recent myocardial infarction or haematocrit (Hct) of less than 30% or diabetes mellitus (Leiria *et al.,* 2011). The patient is more than 65 years of age, had a history of strokes and recent rectal adenocarcinoma, and had an Hct of less than 30%. This sums to the total points of 4, which indicates the highest score of the bleeding risk group of patients. The scoring system of the bleeding risk index is shown in Table 3.

Conclusions

The case highlights the dilemma of anticoagulation therapy in a patient with multiple underlying conditions to prevent a secondary stroke. Despite the nonexistence of antidotes, with the exception of idarucizumab for dabigatran, monitored randomized clinical trials on utilizing new anticoagulant agents in patients with artificial valves are needed to diversify the therapeutic options. Educating patients about the proper use of medication is seemingly the most straightforward strategy to solve this issue. Nevertheless, it could be challenging depending on the background of the patient; the factors include education level, age, and self-discipline. Additionally, the ideal solution is a further investigation to find a new oral anticoagulant drug with stable serum concentration without interactions and a good safety profile.

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