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PROGRESSIVE VENOUS THROMBOEMBOLISM AND WARFARIN-INDUCED SKIN NECROSIS ON BACKGROUND DIABETUS MELLITUS TYPE 2 IN COMBINATION WITH ACCOMPANIED DISEASE: A CLINICAL CASE

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Background. Oral anticoagulants used in clinical practice in atrial fibrillation, deep vein thrombosis, pulmonary embolism (PE), as well as in heart valves protesis, heart thrombosis. Warfarin is the medicine with the largest evidence base and a long history of use more than 70 years. The optimal anticoagulant effect of warfarin is INR from 2,0-3,0 with 70% of measurements (TTR 70%). In one case there is a risk of ischemic stroke in non-compliance, in another - bleeding. Although cutaneous manifestations are rare, however, warfarin-induced skin necrosis is extremely dangerous.

Present`s clinical case of progressive venous thromboembolism on the background of anticoagulant therapy in a 64-year-old woman with comorbid pathology. The described clinical, laboratory and instrumental data, that confirmed thrombotic and thromboembolic complications, which were ineffective in relation to the traditional anticoagulant strategy

Aim: to describe a clinical case and analyze the challenges in diagnosing and treatment of progressive venous thromboembolism in a patient with concomitant diabetus mellitus type 2, obese,cirrhosis of liver , ineffective anticoagulants and developing warfarin skin necrosis.

Materials and methods. The article presents the clinical case of pulmonary embolism, progressive venous thromboembolism in a 64- year -old woman with concomitant diabetus mellitus type 2, obese,cirrhosis of liver that was observed in IUC in the Hospital" Medbud'.

Results. A 64-year-old woman, was hospitalized in the therapeutic department of «Medbud» with a previous diagnosis of cirrhosis of the liver unknown etiology, Child-Pugh class A, hepatolienal syndrome, articular and hemorrhagic syndrome, de novo diabetus mellitus of type 2, paroxysmal atrial fibrillation tachisystolic variant. Preliminarily prescribed dabigatran without "bridge therapy"at a dose of 150 mg twice a day every other day on the recommendation of a gastroenterologist. Suspected pulmonary embolism made adjustments to treatment and anticoagulant therapy was switched from NOAC to UFH, then to LMWH with the addition of warfarin. There was progression of venous thromboembolism in the upper and lower limbs with the appearance of warfarin skin necrosis.

Conclusion. Thus, cumulative influence of start therapy dabigatran without bridge heparin therapy, disturbance dabigatran regimes and drug interaction with glucocorticoids, postinjection phlebitis, liver disease, thrombocytopenia and hypothetical insufficiency antithrombin-III, protein C had influenced on progressive venous thromboembolism on background diabetus mellitus type 2, obese. Warfarin-induced skin necrosis is rare complication, but is often dangerous. In the absence of protein C, antithrombin – III, if possible, consider an alternative anticoagulant. The failures of anticoagulant therapy are not only associated with delays in its appointment, switching of anticoagulants, but also taking into account the drug interaction, concomitant pathology, the choice of the optimal drug and the prediction of its adverse effects.

Key words: pulmonary venous embolism, progressive venous thrombosis, warfarin skin necrosis, diabetus mellitus of type2, cirrhosis of the liver, heparinresistance.

Background. Vitamin K antagonists (VKA), in particular warfarin due to its high efficacy are widely used for both primary and secondary prevention and treatment of thromboembolic complications [2,10,11,12]. The main requirements for any anticoagulant are safety and efficiency. Warfarin is one of the medication that is not always predictable. Having a high bioavailability, the therapeutic effect can be variable and depending on the factors that pharmacokinetics and pharmacodynamics. First, the dose required to provide therapeutic anticoagulation is often high and variable. One of the patients enough to obtain the anticoagulant effect of 2,5 mg of warfarin, in other cases, according to the literature, the dose reached 30 mg. The dose of warfarin in the elderly is not unambiguous. In most cases, the dose in the elderly is lower to maintain the anticoagulant effect, while overweight people require a revision of the dose to increase it. In particular, the recommendations on Pulmonary embolism observed an age-dependent approach (VPE, 2019). The recommended dose of warfarin in people under 60 years - is 10 mg, over 60 years - 5 mg [11]. Dose selection is influenced by different pharmacogenetic patterns, such as gene polymorphism: the pharmacokinetics of VKA depend on the cytochrome CYP2C9 gene, which regulates hepatic metabolism, and the pharmacodynamics of the VKORC1 gene. Secondly, the combined use of other drugs, such as anti-inflammatory, antibiotics, antiplatelet, statins, antidepressants, amiodarone, antifungal drugs, antiretroviral drugs and dietary supplements [13,14]. Changes in diet or drinking alcohol affect the effectiveness of VKA, requiring adjustment of the maintenance dose. The latter, given this variability and the narrow therapeutic window of VKA, monitoring is required to ensure a proper anticoagulant effect within the TTR of 70% [9].

Among the complications, skin manifestations are rare, but warfarin-induced skin necrosis (WINS), which occurs in only 0.01-0.1% of patients receiving warfarin, is often dangerous [1,3]. WINS is more common in women (ratio: 9: 1.3; according to other data, 4: 1), but the cause of the susceptibility is not found out. The first case of WINS was described in 1945 of Flood E.P. et al., who observed breast skin necrosis in a 49-year-old woman, and treated it as migrating thrombosis (thrombophlebitis migrans disseminate). In 1954, Verhagen H. confirmed the correlation of skin necrosis with warfarin (dicoumarol). WINS occurs within 10 days from the start of warfarin therapy, according to the literature, the peak of the lesion occurs on the 3-6th day (83-90% of cases) [4,5].

Aim: to describe a clinical case and analyze the challenges in diagnosing and treatment of progressive venous thromboembolism in a patient with concomitant diabetus mellitus type 2, obese,cirrhosis of liver , ineffective anticoagulants and developing warfarin skin necrosis.

MATERIALS AND METHODS

The article presents the clinical case of pulmonary embolism, progressive venous thromboembolism in a 64- year -old woman with concomitant diabetus mellitus type 2, obese, cirrhosis of liver that was observed in IUC in the Hospital" Medbud".

Case report. A 64-year-old woman was hospitalized in the therapeutic department of «Medbud» with a previous diagnosis of cirrhosis of the liver unknown etiology, Child-Pugh class A. Patient had hepatolienal syndrome, de novo diabetus mellitus of type 2 in subcompensation stage, steatohepatosis, paroxysmal atrial fibrillation tachisystolic variant. Patient complained of severe pain in the lower and upper extremities, which intensified with the slightest movement; general weakness, nausea, pain in the right site under the ribs and fever.

Anamnesis: patient before admitted to the hospital treated for 2 weeks in the endocrinology department of another clinic, where dabigatran was prescribed at a dose of 150 mg twice a day, probably due to the paroxysm of atrial fibrillation. Preliminary administration of Low molecular weight Heparin (LMWH) before the appointment of dabigatran in the medical history is not documented. According to the patient, on the 2-3rd day after the appointment of dabigatran, there was pain in the lower and upper extremities, the intensity of which increased with the slightest movement. Isolated haemorrhagic rashes appeared on the skin of the forearms. In addition to

dabigatran 150 mg twice daily the patient received enalapril 5 mg, atorvastatin 20 mg, and metformin 1000 mg, amiodaron 400 mg [14].

Objectively the patient's condition severe. BMI 35kg/ m2. Position in bed is passive due to severe pain sharply limited range of motion in the upper and lower extremities, on palpation of the muscles of the extremities - sharp pain. Hemodynamic stable: pulse 105/ min, BP 134/74 mm Hg. Heart borders are slightly shifted to the left. Sound heart tones, tachycardia. Percussion shortening of percussion tone in the lower parts on both sides. Auscultations breathing is decreased in the lower parts on both sides, liver is +3 sm, sensitive, the edge is rounded. Joints of normal configuration, color, warm to the touch, there is a sharp limitation of movement due to severe pain.

Haemorrhages are noted on the forearm, which are regarded as a thrombohemorrhagic syndrome, taking into account both the underlying disease (liver cirrhosis) and using of dabigatran. The gastroenterologist recommended taking dabigatran every other day. Differential diagnosis was performed between polymyositis, rhabdomyolysis, idiopatic myopathy, Hyena-Barre syndrome, polyneuropathy of diabetic origin, acute spinal circulatory disorders, fracture of the femoral neck. The patient was consulted by a neurologist, traumatologist. Peripheral neuromyopathies and pathology of the musculoskeletal system were excluded. Swelling of the left shoulder is caused by post-injection phlebitis. Ultrasound of the vessels of the upper extremities revealed subcutaneous thrombosis of the v.cephalic on the left in the lower third due to post-injection thrombophlebitis (Fig. 1).

Laboratory examination was scheduled to verify diffuse connective tissue disease, vasculitis, antiphospholipid syndrome.

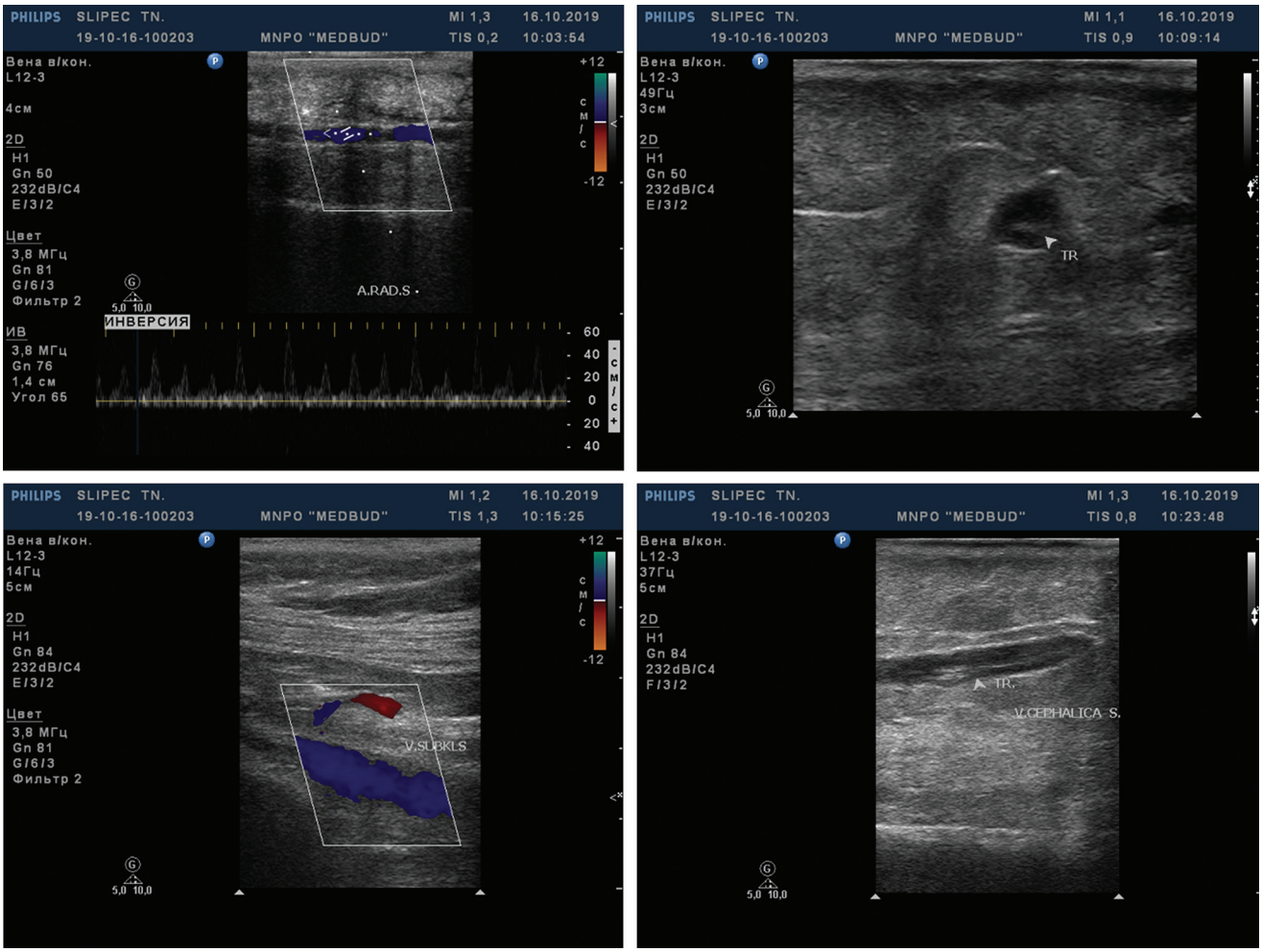

Fig. 1. Subcutaneous thrombosis v.cephalica sinistra

Given that upper extremity thrombosis occurred with dabigatran, the regimen was changed from oral anticoagulant to LMWH (enoxaparin at a dose of 0.4 mg twice a day), which according to the new recommendations for venous thrombosis had certain preferences over Heparin (NFH). Based on the data of the clinical picture - muscle pain, stiffness, and laboratory control- CRP 72.74 mg / l, rheumatoid factor 76.7 IU / ml, ALT 13 IU / l, AST 18 IU / l, CPK 91, 9 units / l, prescribed proton pump inhibitors and corticosteroids - esomeprazole 40 mg / day, dexamethasone at a dose of 16 mg / day, which was accompanied by clinical improvement with a decrease in the intensity of muscle and joint syndrome from the first day of corticosteroids, temperature normalization. The patient began to move independently, the movements were carried out in full.

According to fibroelestography: the right lobe of the liver with signs of fatty hepatosis 1 st, fibrosis according to Metavir 4 degrees.

On the 6th day of hospitalization appeared paroxysmal tachysystolic form of atrial fibrillation (CHADSVasc-6 points, HASBLED-5 points) and the resulting unmotivated dyspnea, the patient was transferred to the intensive care unit (ICU). When assessing the probability scales of pulmonary embolism on the WELLS scale – 7,5 points (high risk): on the risk scale of 30-day hospital mortality PESI - 198 points (grade 5) is very high risk.

Given the concomitant pathology of liver cirrhosis and the fact that pulmonary embolism occurred on the background of taking LMWH in therapeutic doses and available contraindications to thrombolysis, it was decided to replace enoxaparin with NFH. The level of creatinine 95 μmol/l, urea 8,1 mmol/l, troponin 0,71 ng/ml, D-dimer 627 ng/ml, glycemia 5,4 mmol/l. Indicators of coagulogram APTT-35s., Fibrinogen 3,5 g/l, INR 1,8. Despite NFH therapy, the development and progression of thrombosis of the right upper extremity was noted. According to ultrasound: thrombosis of v. cephalica dex., complete thrombosis of v. basilica dex. in the lower and middle third. Partial thrombosis of v. cephalica sin. persisted in the upper and middle third of the left upper limb. Against the background of heparin therapy revealed clinical signs of venous thrombosis of the left lower extremity, which were confirmed by sonographic examination.

During dynamic control, the D-dimer increased insignificantly to values of 685 ng/ml. After a two-day infusion of NFH on the background of which thrombocytopenia (70 x109/l) was noted, it was replaced by LMWH (enoxaparin 0,8 bid). Given that thrombocytopenia is an unfavorable prognostic factor for the initiation of thrombosis, on the other hand, it was important to exclude or confirm the antiphospholipid syndrome. On the 4th day of stay in the intensive care unit, platelet levels were restored. According to the results of the laboratory study, systemic connective tissue diseases, antiphospholipid syndrome, systemic vasculitis were excluded. Prescribed therapy

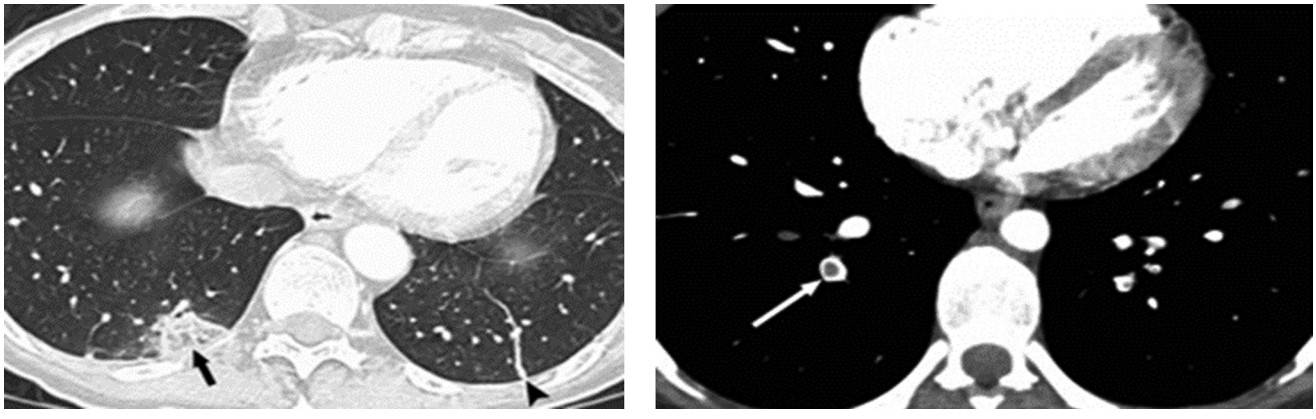

Fig. 2. MSCT with contrast confirmed bilateral pulmonary embolism of segmental and small branches of the pulmonary artery. On Echo-CG moderate pulmonary hypertension (pulmonary artery pressure – 55 mm Hg), RV – 35 mm, E/A ratio 2,2.

required correction of carbohydrate metabolism by selection of insulin doses.

The general condition of the patient has improved: consciousness is clear, the patient is contact, hemodynamically stable, movements within the bed are performed in full without pain, RR 20, O2 Sat 96%. However, despite taking LMWH in therapeutic doses, the picture of venous thromboembolism of the veins of the left lower extremity continued to grow and ultrasound of the veins revealed: complete thrombosis of the external iliac, common and superficial femoral veins, popliteal vein. It was decided to add warfarin under the control of INR (until the level of 2.0-3.0) to prevent generalization of thrombosis. Thus, the picture of migrating venous thrombosis of the upper and lower extremities with pulmonary embolism was observed.

The initial reception of VKA from a dose of 2,5 mg with gradual increase in a dose under control of INR to 5 mg is begun. On the 4th day of warfarin in the patient on the right upper extremity, the rash of hemorrhagic nature rapidly increased and turned into subcutaneous hematomas. Significantly increased the incidence of renal and hepatic insufficiency, appeared a neurodeficiency - 9 points of GCS; glycaemia 7.4 mmol/l, creatinine level 195 μmol/l, urea 18.7 mmol/l, levels of transaminases, albumin and total serum protein within the reference values. In the general analysis of blood hemoglobin level - 84 g/l with anisocytosis and leukocytosis, 12,5 × 109/l , platelet levels 127 × 109/l. Given the anamnestic data, the objective status of the patient, namely liver disease, the picture of severe progressive thrombosis despite anticoagulant therapy and the appearance of hemorrhagic rash, which is regarded as warfarin necrosis of the skin, there was an assumption of a possible deficiency of protein C, which are synthesized at the liver. Probably antithrombin failure in patient with liver cirrosis initiated heparin resistance and migrating venous thrombosis(6,8).

After immediate discontinuation of warfarin, a constant infusion of NFH was restarted and vitamin K and infusions of single-group fresh-frozen plasma were administered. After additional examination, cerebrovascular disorders were ruled out. The phenomena of acute renal failure and acute cardiovascular insufficiency, which could not be further corrected, increased significantly. Hemorrhagic-necrotic changes of the upper right limb are presented (Fig. 3).

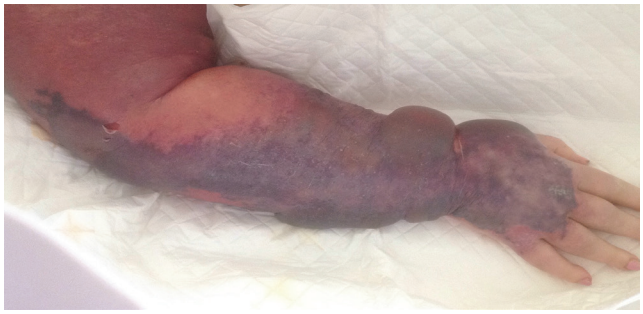

Fig. 3. Warfarin skin necrosis.

DISCUSSION

Hypercoagulation inherent from the first days of warfarin is offset by the simultaneous appointment of LMWH and only when the INR reaches 2,0-3,0 LMWH are canceled. A similar tactic applies to dabigatran, in contrast to rivaroxaban and apixaban, which are prescribed immediately for low-risk pulmonary embolism. Dabigatran is used after a five-day LMWH administration.

The pathogenesis of warfarin-induced skin necrosis (WINS) is not fully understood, there are possible pathophysiological mechanisms, such as thrombosis, direct toxic effect, factor VII and protein C deficiency, hypersensitivity, hemorrhage. It was found that while taking warfarin there is an imbalance of vitamin-K-dependent procoagulant factors of coagulation and anticoagulant proteins C and S, which can cause paradoxical transient hypercoagulation, especially in the first days of its use [1, 3]. Thus, warfarin is not prescribed as monotherapy, but simultaneously with heparin. The early suppressive effect of warfarin on protein C is not able to compensate for the anticoagulant effect caused by a decrease in other vitamin K-dependent factors (II, IX and X) [4, 5]. The result is transient local hypercoagulation, which can cause thrombosis of capillaries, venules and veins of the skin, subcutaneous fat and their necrosis.

The literature proposes a hypothesis about the direct toxic effect of warfarin on the endothelium as one of the mechanisms of WINS development

[1, 3]. However, this hypothesis has not been experimentally confirmed. It has been suggested that hypersensitivity reactions to warfarin may be one of the causes of WINS, but this is unlikely. According to the results of allergy skin tests with the drug in patients with a «pathology» allergy history, no hypersensitivity reactions of the immediate and delayed type were detected. It should be noted that conditions characterized by low levels of protein C include: VKA therapy, liver disease, vitamin K deficiency, acute thrombosis, sepsis, disseminated intravascular coagulation (DIC) syndrome, hemopoetic stem cell transplantation [5, 9, 10].

In this clinical case, the basis of the pathogenesis of progressive, migratory thrombosis is most likely a hypothetical deficit not only of protein C synthesis, but also AT-III due to liver disease, which caused the inefficiency of NFH. The so-called "clinical heparin resistance", in particular in our patient, is probably due to impaired synthesis of AT-III, not only due to liver disease but also spleen, renal clearance [8]. It occurs in about 22%. Increased thrombogenicity at some stage was maintained by thrombocytopenia, which was due to the underlying disease and could be initiated by the introduction of NFH. Although these complications occur in only 1%, but require a review of treatment tactics.

Unwanted provoking factors of progressive thrombosis were forced immobilization of the patient due to severe pain, corticosteroids, violation of the regimen of dabigatran (it is unacceptable to take the drug every other day), post-injection thrombophlebitis, type 2 diabetes mellitus. It should be noted that skin necrosis develops mainly in areas of overdeveloped subcutaneous fat, such as buttocks, thighs, abdomen and chest, sometimes observed on the back, arms, legs, face.

Localization is more often unilateral, but in 30-35% of cases – bilateral and with multiple localizations was observed. In 80% of patients, WINS is observed in the lower half of the body. In women, it is most often the mammary glands, then the buttocks and thighs. In men, skin lesions in the chest are rare, but the pathological process may involve the skin of the penis. The skin of the torso, face and limbs can be equally affected in both men and women [3]. In case of warfarin necrosis, VKA should be stopped immediately to prevent the progression of necrosis and NFH or LMWH should be prescribed until the affected areas of the skin improve and the skin lesions heal. In addition, parenteral vitamin K and fresh-frozen plasma are administered to reduce the effects of warfarin and restore the level of vitamin K-dependent coagulation factors and proteins C, S.

This tactic was chosen in the patient. It is possible to use protein C concentrate (in patients with proven deficiency), as well as prostacyclin, the positive effect of which is clinically and histologically proven; concentrate of 4-component prothrombin complex (PCC), which contains coagulation factors (II, VII, IX and X) and proteins C, S, which, similar to fresh-frozen plasma, reduces INR and increases the concentration of proteins C and S faster and more efficiently at a lower volume.

The literature provides data on the use of activated protein C and AT-III (10). If necessary, warfarin can be resumed, in these cases it is recommended to titrate the drug starting from lower doses (with a gradual increase of 1-2 mg/day) with concomitant use of heparin (bridge therapy) and its subsequent cancellation only when reaching the target level of INR. Monitoring of the patient's condition is mandatory. These data are highlighted by the recommendations of the American College of Thoracic Surgeons (ACCP) in patients taking warfarin for the treatment of deep vein thrombosis [9].

The goal of this warfarin regimen is to achieve a balanced reduction in protein C levels and coagulation factors. Prolonged heparin therapy and LMWH may be prescribed, but possible complications such as osteoporosis and thrombocytopenia should be considered. Despite drug therapy, more than 50% of patients with WINS require surgery. Surgical treatment of the affected areas and staged necrectomy are required, in some cases there may be a need for dermoplasty or even amputation of the affected areas.

CONCLUSION

Thus, cumulative influence of start therapy dabigatran without bridge heparin therapy,

disturbance dabigatran regimes and drug interaction with glucocorticoids, postinjection phlebitis, liver disease, thrombocytopenia and hypothetical insufficiency antithrombin-III, protein C had influenced on progressive venous thromboembolism on background diabetus mellitus type 2, obese and liver disease. Warfarin-induced skin necrosis is rare complication, but is often dangerous. In the absence of protein C, antithrombin – III, if possible, consider an alternative warfarin anticoagulant. The failures of anticoagulant therapy are not only associated with delays in its appointment, switching of anticoagulants, but also taking into account the drug interaction, concomitant pathology, the choice of the optimal drug and the prediction of its adverse effects.

Conflict of interest. Authors declare no conflict of interest

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ПРОГРЕСУЮЧА ВЕНОЗНА ТРОМБОЕМБОЛІЯ ТА ВАРФАРИН-ІНДУКЦІЙНИЙ НЕКРОЗ ШКІРИ НА ФОНІ ЦУКРОВОГО ДІАБЕТУ 2 ТИПУ В ПОЄДНАННІ ІЗ СУПУТНІМ ЗАХВОРЮВАННЯМ: КЛІНІЧНИЙ ВИПАДОК

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Актуальність. Пероральні антикоагулянти широко застосовуються в клінічній практиці при фібриляції передсердь, тромбозах глибоких вен кінцівок, тромбоемболії легеневої артерії, а також при протезуванні клапанів серця, тромбах в порожнинах серця, тощо. Варфарин є препаратом із найбільшою доказовою базою і давньою історією застосування більш ніж 70 років. Оптимальним антикоагулянтним ефектом варфарину вважається діапазон досягнутого МНО від 2,0-3,0 із 70% вимірів (TTR 70%), а при недотриманні - в одному випадку існує ризик ішемічного інсульту, в іншому – кровотеч. І хоча шкірні прояви зустрічаються рідко, проте вкрай небезпечним є варфарин-індукований некроз шкіри. Наводимо клінічний випадок прогресуючого венозного тромбоемболізму на фоні антикоагулянтної терапії у хворої 64-років з коморбідною патологією. Описані клінічні, лабораторні та інструментальні дані, підтвердили тромботичні та тромбоемболічні ускладнення, які виявились неефективними щодо традиційної антикоагулянтної стратегії.

Ціль: описати клінічний випадок та проаналізувати проблеми діагностики та лікування прогресуючої венозної тромбоемболії у хворої із супутнім цукровим діабетом 2 типу, ожирінням, цирозом печінки, неефективністю антикоагулянтної терапії та розвитком варфаринового некрозу шкіри.

Матеріали та методи. У статті наведено клінічний випадок тромбоемболії легеневої артерії, прогресуючої венозної тромбоемболії у жінки 64 років із супутнім цукровим діабетом 2 типу, ожирінням, цирозом печінки, що спостерігався у клініці лікарні «Медбуд».

Результати. Жінка 64 років госпіталізована в терапевтичне відділення клініки «Медбуд» з попереднім діагнозом: цироз печінки невідомої етіології, клас А за Чайлд-П'ю, гепатолієнальний, суглобово-геморагічний синдром, цукровий діабет 2 типу de novo, пароксизмальна форма фібриляції передсердь тахісистолічний варіант. Попередньо за рекомендацією гастроентеролога через день призначили дабігатран по 150 мг двічі на добу, без попередньої « терапії моста» гепарином. При підозрі на тромбоемболію легеневої артерії внесено корективи в лікування та здійснено перехід антикоагулянтної терапії з НОАК на НФГ, потім на НМГ з додаванням варфарину. Проте, спостерігалось прогресування венозного тромбозу верхніх та нижніх кінцівок. з появою варфаринового некрозу шкіри.

Висновки. Таким чином, кумулятивний вплив стартової терапії дабігатраном без «терапії моста» гепарином, порушення режимів застосування дабігатрану (через день)та міжлікарської взаємодії, наявність постін'єкційного флебіту, захворювання печінки, тромбоцитопенія та гіпотетична недостатність антитромбіну-ІІІ, протеїну С вплинули на прогресуючу венозну тромбоемболію на фоні цукрового діабету 2 типу, ожиріння, що ймовірно стало причиною» резистентності до гепаринів».Некроз шкіри, викликаний варфарином, є рідкісним ускладненням, але часто небезпечним. Слід при відсутності або недостатності протеїну С, антитромбіну – ІІІ, якщо можливо, розглянути альтернативний до варфарину антикоагулянт. Невдачі через неефективність антикоагулянтної терапії пов'язана не тільки із запізненням у її призначенні, невиправданою заміною антикоагулянтів, а й з урахуванням міжлікарської взаємодії, супутньої патології, вибором оптимального препарату та прогнозуванням його побічних ефектів.

Ключові слова: тромбоемболія легеневої артерії, прогресуючий венозний тромбоз, варфариновий некроз шкіри, цукровий діабет 2 типу, цирроз печінки, гепаринрезистентність.