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Case Report

Warfarin without Therapeutic Monitoring Is a Rodenticide, but This Time It Kills the Patient: A Warfarin Toxicity Case Report

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ABSTRACT

According to the American Association of Poison Control Centers (AAPCC), 761 single exposures to the pharmaceutical warfarin were reported in 2021, accounting for more than 10 percent of anticoagulant cases. The cost and mortality caused by warfarin toxicity are very high and usually incurable and fatal. The most important action in the field of warfarin toxicity is to prevent its occurrence. To emphasize how warfarin toxicity occurs, a case is introduced in this regard. A 61-year-old man is found unconscious with a seizure on the street and transported to the hospital by Emergency Medical Services (EMS). In the emergency car, he received a diazepam injection for generalized seizures. His vital signs in the postictal state were as follows: blood pressure 82/44 mmHg, pulse rate 91 bpm, and oxygen saturation (SaO2) 93%. His past medical history includes an ischemic stroke and a myocardial infarction 12 years ago. He underwent Mitral valve repair 11 years ago and a mechanical-type Mitral valve replacement 2 years ago. After undergoing mitral valve replacement surgery, he continued taking warfarin and aspirin for 2 years without consulting a cardiologist or undergoing PT and INR tests. As a result, he suffered a massive intracerebral hemorrhage when his INR level rose above 6. It's important to note that he has no history of depression or suicide attempts. After experiencing decreased consciousness and seizures, he was quickly intubated. A brain CT scan revealed extensive evidence of intracerebral hemorrhage, and he was then transferred to the operating room for craniotomy. To manage the bleeding and because Prothrombin complex concentrate (PCC) was not available, the patient received two grams of fibrinogen, two units of Fresh Frozen Plasma (FFP), 10 mg of vitamin K, and one unit of Packed Red Blood Cells. Unfortunately, after a month-long stay in the ICU, the patient passed away as a result of Ventilator-associated pneumonia (VAP) and sepsis.

The authors declare no conflicts of interest.
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Introduction

The first report of sweet clover poisoning was in February 1933 in California cattle. It was manifested by a hemostatic disorder, prolongation of coagulation time, subcutaneous bleeding, and hemorrhagic abortions. Sweet clover poisoning is caused by dicumarol [1]. Therefore, an initial idea of warfarin originated from the farm. Warfarin was first marketed as a rodenticide in 1948 and was approved as a human drug in 1954 [2]. Warfarin is derived from WARF (Wisconsin Alumni Research Foundation) and –arin from coumarin [3]. Warfarin inhibits the synthesis of anticoagulants by preventing the carboxylation of vitamin K-dependent coagulation factors II, VII, IX and X to prevent blood clotting, and thrombosis [4]. At least 1-3% of warfarin users experience fatal bleeding.

The most efficient approach to counteract the effects of warfarin is the administration of a four-factor prothrombin complex concentrate (PCC). Presently, emergency physicians in the United States have access to various treatment options, including fresh frozen plasma, recombinant factor VIIa (rFVIIa), factor eight inhibitory bypass, or trifactor PCC, which can be given simultaneously with vitamin K [5]. PCC is derived from human plasma. The levels of coagulation factors in PCC are roughly 25 times greater than those found in plasma, allowing for its administration in smaller quantities to attain the intended clinical outcome [6].

The simultaneous use of aspirin and warfarin doubles the risk of warfarin bleeding [7].

Case Report

A 61-year-old man is found unconscious with a seizure on the street and transported to the hospital by Emergency Medical Services (EMS). In the emergency car, he received a diazepam injection for generalized seizures. His vital signs in the postictal state were: blood pressure 82/44 mmHg, pulse rate 91 bpm, and oxygen saturation (SaO2) 93%. His past medical history includes hypertension (HTN), ischemic stroke, and myocardial infarction about 12 years ago. The patient's heart surgery records indicate a mitral valve repair 11 years ago and a mechanical-type mitral valve replacement two years ago. After the mitral valve replacement surgery, he continued to take warfarin and aspirin for two years without visiting a cardiologist or undergoing Prothrombin time (PT) and international normalized ratio (INR) blood tests. He was addicted to opium and smoked, but had no history of depression or suicide attempts. After a decrease in consciousness and seizures, he was promptly intubated. After a brain CT scan, extensive evidence of intracerebral hemorrhage was observed (Figure1). He underwent a craniotomy and hematoma irrigation in the operating room. To control the bleeding and due to the unavailability of PCC, he was given two grams of fibrinogen, two units of FFP, 10 mg of vitamin K, and one unit of packed red blood cells. But he had recurrent Intracerebral hemorrhage. The results of the laboratory data at the time of admission are presented in (Table 1). Finally, after one month of being hospitalized in the ICU, he passed away due to ventilator-associated pneumonia (VAP) and sepsis.

Table 1- Laboratory testing upon admission

Test	Report	Reference range
Hemoglobin (gr/dl)	12.2	13.5-18
Platelet ($*10^3$ /µl)	194	150-400
AST(U/L)	19	Up to 38
INR	6.6	
Total Bilirubin	1.83	0.3-1.2
Creatinine (mg/dl)	1.1	0.6-1.4

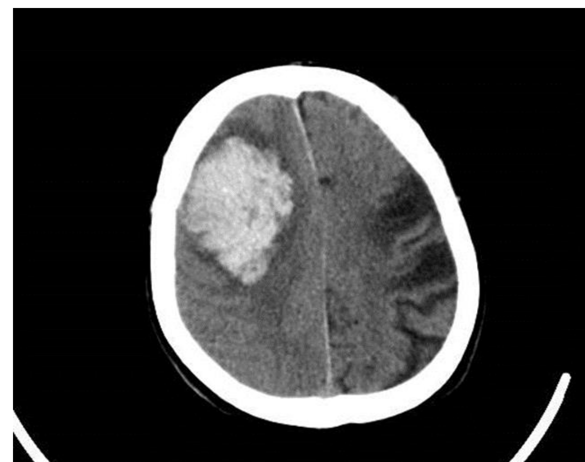

Figure 1- Brain CT ScaN OF PATIENT

Discussion

Nearly 7000 cases of ICH happen in the US every year as a result of oral anticoagulants [8]. ICH affects approximately 29.9 out of every 100,000 individuals within a year [9]. A cohort study investigated AF patients with warfarin-induced intracranial hemorrhage and found that 90% of these patients died or were severely injured [10]. Many studies concluded that the combination of aspirin (regardless of its dose) and warfarin increased the risk of bleeding [11]. Addition of aspirin to warfarin in elderly patients can increase the risk of bleeding by 40% [12]. While the risk of bleeding increases with the use of warfarin and aspirin in patients with mechanical valves, it reduces the rate of stroke and death [13]. Age older than 75 years, hypertension, intensity of anticoagulation, and previous cerebral ischemia were all associated with ICH [14-15]. In this case, the patient had evaluated blood pressure but didn't take any medication Furthermore, a randomized trial found that reducing blood pressure can decrease the occurrence of ICH in patients receiving anticoagulants or antiplatelets [16]. The most significant risk factor for bleeding caused by warfarin is supratherapeutic INR and failure to perform therapeutic

drug monitoring (TDM) [17]. Establishing the patient's adherence to coagulation tests is necessary to ensure the therapeutic and safety effects of the patient. Creating insight and adherence to treatment in the patient is a teamwork between the patient, doctor, nurse, and pharmacist [18]. Breaking the bond between the patient and the treatment team leads to breaking the bond of his/her life. Therefore, the doctor, nurse, and pharmacist should never abandon the patient, especially if he/she is taking warfarin.

Conclusion

The importance of TDM for a patient taking warfarin cannot be overstated. It is crucial for ensuring the patient's safety and well-being and can be considered as vital as safeguarding the patient's life.

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