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Case Report

Massive Gastrointestinal Bleeding, Consequences Interactions of Apixaban, Diltiazem and Aspirin: Case Report

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ABSTRACT

Anticoagulation is the cornerstone of preventing thrombosis. Following the aging of society and the greater use of anticoagulant drugs, we see more serious complications in this group. The reduced occurrence of significant bleeding represents a notable benefit of direct oral anticoagulants (DOACs) in comparison to vitamin K antagonists. However, the unavailability of Andexanet alfa and Idarucizumab complicates the management of bleeding associated with DOACs. This case describes a 69-year-old man who presented with massive gastrointestinal bleeding, hemorrhagic shock, and loss of conciseness. He has been taking apixaban 2.5 mg twice a day, aspirin 80 mg once a day, and diltiazem 60 mg three times daily. Bleeding was controlled through transfusion of two units of fresh frozen plasma, five units of packed cell, four units of platelet, and tranexamic acid injection. Although hemorrhagic shock was successfully managed, he unfortunately passed away after three weeks of hospitalization following Ventilator-associated pneumonia and sepsis. In this case, we discuss the importance of the drug interaction of apixaban, diltiazem, and aspirin.

Introduction

Direct oral anticoagulants (DOACs) have received approval from the US FDA for various medical applications [1]. One significant benefit of DOACs in comparison to vitamin K antagonists is the lower occurrence of major bleeding events, along with the ease of perioperative management [2]. The mechanism of gastrointestinal bleeding with DOACs can be explained by its pharmacokinetics. The bioavailability of DOACs varies from 50-80% and the remaining unabsorbed drug in the lumen can exacerbate bleeding from existing lesions and other mucosal breaks [3]. Diltiazem by inhibiting P-glycoprotein (P-gp) and cytochrome P450 (CYP) causes an increase in area under the concentration versus time curve (AUC) and maximum serum concentration (Cmax) of apixaban by 40% and 31%, respectively [4]. It is recommended to use metoprolol instead of diltiazem to control the ventricular rhythm in patients taking DOACs [5]. Simultaneous use of aspirin along with apixaban leads to a significant increase in the risk of bleeding [6]. A bleeding event is classified as major bleeding, if it occurs in a critical area or organ, leads to a decrease in hemoglobin of 2 g/dL or

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more, requires transfusion of 2 or more units of red blood cells, or causes hemodynamic instability [7].

Case Report

A 69-year-old man was admitted to the emergency department (ED) with hemoptysis, coffee-ground vomiting, and melena. His medical history includes heart failure with reduced ejection fraction (HFrEF), Chronic obstructive pulmonary disease (COPD), ischemic heart disease (IHD), Diabetes mellitus (DM), hypertension (HTN), and coronary artery bypass graft (CABG) 10 years ago. He was taking empagliflozin, sacubitril-valsartan, eplerenone, metformin, digoxin, apixaban 2.5 mg twice a day, aspirin 80 mg once a day, and diltiazem 60 mg three times daily. The vital signs in admission were pulse rate=106 bpm, BP=72/41 mmHg, temperature (T)= 37°C, SPO2=95% and Hemoglobin (Hb) =7 g/dL (Table 1). Hemorrhagic shock and extensive bleeding were controlled by transfusion of two units of Fresh frozen plasma (FFP), five units of packed cell, and four units of platelet. The patient received continuous infusion of pantoprazole, octreotide, norepinephrine, and two liters of isotonic solution of sodium chloride for fluid resuscitation. He was intubated and transferred to the operating room to investigate the source of bleeding and underwent a laparotomy. No signs of liver disease were found, but several erosions around the antrum were observed. He became unstable and had a cardiac arrest, but Cardiopulmonary resuscitation (CPR) was successful for 5 minutes. He was then transferred to the Intensive Care Unit (ICU), where he died three weeks later after experiencing acute decompensated heart failure, ventilator-associated pneumonia, and septic shock, despite successful management of the hemorrhagic shock.

Table 1- Laboratory testing upon admission

Test	Report	Reference range
Hemoglobin (gr/dl)	7.4	13.5-18
Platelet (*10^3 /µl)	120	150-400
AST(U/L)	17	Up to 38
ALT (U/L)	14	Up to 41
Creatinine (mg/dl)	1.3	0.6-1.4
Urea (mg/dl)	99	19-44
PTT	32.6	25-40
INR	1.65	0.8-1.1

Discussion

Patients with heart failure (HF) are at a higher risk of complications caused by drug interactions [8]. All DOACs have renal elimination and patients with HF tend to have a higher prevalence of renal dysfunction. As a result, a higher risk of bleeding compared to warfarin may be expected in some subsets of patients with HF [9]. In the ARISTOTLE trial, it was shown that factors such as DM, age, and the simultaneous use of aspirin can increase the risk of bleeding caused by DOACs [10]. The ROCKET AF trial also revealed that COPD is a risk factor for bleeding in patients taking rivaroxaban [11]. Drug interaction factors in the rate of bleeding events should not be overlooked. Moderate inhibitors of CYP3A4 may elevate the serum levels of rivaroxaban and apixaban. A retrospective study on patients with atrial fibrillation which were receiving diltiazem and apixaban, showed a significant risk of bleeding incidence [5]. A retrospective cohort study of patients receiving apixaban or rivaroxaban showed that coadministration with diltiazem, verapamil, and amiodarone increases the risk of any bleeding [12].

The patient's serum creatinine (SCr) level was 1.3 mg/dL, and both the glomerular filtration rate (GFR) and liver function tests (LFT) were normal at admission. Therefore, neither hepatic nor renal risk factors contributed to the patient's condition. The patient's comorbidities, including DM, HTN, smoking, and COPD, were crucial factors leading to major bleeding events.

The prompt initiation of tranexamic acid for counteracting the effects of DOACs in patients experiencing life-threatening hemorrhage is linked to a reduction in bleeding [13-16]. Injectable tranexamic acid, one gram, was prescribed to the patient three times daily. While specific antidotes such as andexanet alfa or unspecific hemostatic agents like prothrombin complex concentrate (PCC), activated PCC (aPCC), or recombinant factor VIIa (rFVIIa) can achieve apixaban reversal [17], these options were not available, so alternative treatments were used. FFP can neutralize the effects of DOACs-mediated factor II or factor X inhibition [17]. However, a large volume of FFP is required to provide adequate amounts of factors II and X, which can be challenging in patients with HF. In this case, a total of 4 units of FFP were administered. Additionally, to maintain the patient's hemoglobin level above 7 g/dL, a total of 5 units of packed red blood cells were administered, successfully controlling the massive gastrointestinal bleeding.

Conclusion

This report reveals the significant impact of minor bleeding risk factors when combined, potentially leading to fatal events. It emphasizes the importance of closely monitoring bleeding risk factors and drug interactions during the administration of DOACs.

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