sciendo

10.2478/AMB-2024-0024

CASE REPORT

SEVERE SUBCONJUNCTIVAL BLEEDING IN A PATIENT WITH CONCOMITANT USE OF WARFARIN AND VALPROIC ACID

R. T. Pinzon[1,3], M. Afifudin[1,2], A. Digdoyo[1]

[1]Faculty of Medicine, Duta Wacana Christian University – Yogyakarta, Indonesia
[2]Department of Ophthalmology, Bethesda Hospital – Yogyakarta, Indonesia
[3]Department of Neurology, Bethesda Hospital – Yogyakarta, Indonesia

Abstract. *Drug interactions with vitamin K antagonist may involve antiepileptic drug. Numerous antiepileptic drugs are strong inducers or inhibitors of liver enzymes and affect warfarin metabolism, including valproic acid, which is capable of displacing warfarin from the protein binding site. Although this type of drug interaction is less widely recognized, it is a phenomenon that causes significant changes in the INR. We report a case of severe subconjunctival bleeding in patient with concomitant use of warfarin and valproic acid. The management include cessation of the drug, conservative eye treatment, and vitamin K. The case was fully resolved.*

Key words: *warfarin, divalproex acid, subconjunctival bleeding, stroke*

Address for correspondence: *Rizaldy Taslim Pinzon, Faculty of Medicine, Duta Wacana Christian University, Yogyakarta, Indonesia, 55224, email: drpinzon17@gmail.com*

Received: *26 January 2024;* ***Revised/Accepted:*** *22 April 2024*

INTRODUCTION

Elderly patients show an increase in multiple comorbidities associated with polypharmacy, particularly in older patients with epilepsy and post-stroke epilepsy [1]. Antiepileptic drugs (AEDs) and concomitant use of other drugs can have significant clinical effects due to their interaction with liver enzyme function and shifts in protein binding sites [2].

In previous studies, the potential interaction between valproic acid (VPA) and warfarin was rarely reported or discussed [1, 2]. The use of these two medications may be very uncommon. We report a case with interaction between oral valproic acid and oral warfarin that resulted in a substantial increase in the international normalized ratio (INR) and severe subconjunctival bleeding.

CASE PRESENTATION

A male patient in his 70s was admitted to the neurological ward due to recurrent stroke, general tonic-clonic seizure (GTCS), and atrial fibrillation. An infarction stroke from cardioembolic had been diagnosed, and the patient was treated with warfarin. The past medical history was otherwise unremarkable, except stable post stroke condition. For the secondary prevention of embolic events resulting from paroxysmal atrial fibrillation (AF), a prescription for 2 mg of warfarin was given. The patient's INR was not observed for six months, during which time there was no significant bleeding.

On the day of admission, while en route to a brain computed tomography (CT) scan, the patient was given 10 mg of diazepam intravenously to stop a

five-minute GTCS. Status epilepticus (SE) was the working diagnosis, and phenytoin was administered intravenously as a loading dosage to treat the recurrent episode. The patient remained physically well during interictal phase. As soon as the patient was stable and conscious, oral valproic acid was prescribed twice daily. The initial INR of 1.7 was used as an excuse for continuing oral warfarin. In addition, the patient was taking 2.5 mg of bisoprolol tablet and 40 mg of oral isosorbide mononitrate sustained release tablet each day.

Routine laboratory tests on the second day of hospitalization revealed otherwise normal results, except for a slight increase in leucocyte count. ECG showed paroxysmal atrial fibrillation with a ventricular rate of 78 bpm. The oral valproate sodium was continued. Seizures ceased from the start of phenytoin infusion.

During the 4th hospital admission, the patient developed a significant ecchymosis and severe subconjunctival bleeding (Fig. 1). The INR was found to be 8.5 and INR 6 hours later was 7.2. We rapidly stopped the oral warfarin. We immediately gave vitamin K injection 3 times daily after being consulted by ophthalmologist, and closely monitored the patient. His condition was otherwise stable. His Glasgow Coma Scale score was 15. A third INR showed a value of 6.4. After consulting with an ophthalmologist, the patient received intravenous vitamin K, and the INR level 24 hours later was 2.16. The patient showed no signs of bleeding and remained to be asymptomatic. The eye treatment includes chloramphenicol eye drops and close monitoring of the subconjunctival bleeding.

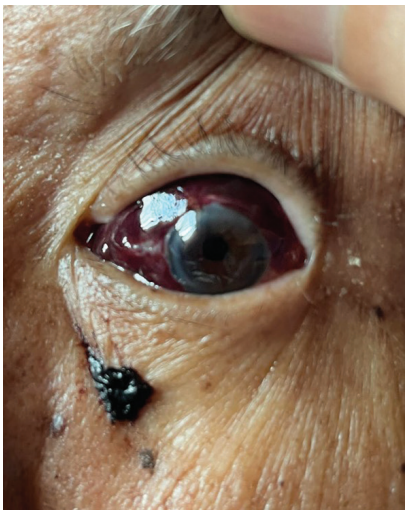

Fig. 1. Severe subconjunctival bleeding and high INR

After careful examination of the drug–drug interactions we suspected that concomitant use of valproic acid was responsible for the event. The Naranjo scale from the use of valproic acid was possible. We stopped the concomitant use of valproic acid and switched to oral Levetiracetam that has less clinical significant interaction. Warfarin was carefully started again at a dose of 1 mg based on the observation of an INR of 2.1. It titrated back to 1.5 mg with steady monitoring of the INR levels to ensure a value between 2 and 3. We continued the eye medication. We carefully observed the visual acuity, and there was no significant decrease of it. The patient was discharged with moderate disability from stroke, and significant resolution of subconjunctival bleeding (Fig. 2). One week after hospital discharge, in outpatient clinic the subconjunctival bleeding was significantly resolved.

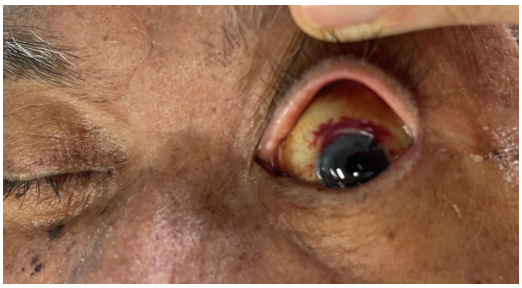

Fig. 2. At hospital discharge, the subconjunctival bleeding was almost completely resolved

DISCUSSION

The comorbidities linked to polypharmacy are becoming more prevalent among elderly [1]. Co-administration of other medications with antiepileptic drugs (AEDs) may have clinically significant effects. There are seldom reports or discussions of the possible interaction between warfarin and valproic acid (VPA) [3]. Before this case, some reports mentioned the possibility of warfarin interacting with a variety of AEDs, such as carbamazepine, phenytoin, and others. Warfarin and VPA are suspected to have drug–drug interactions that have been suggested by another review [3, 4]. There is not much discussion of real-world case reports that show how these two medications interact.

There have been prior reports of comparable cases where the combination of warfarin and valproate resulted in an unexpected and significant increase in INR levels [3, 4, 5]. Our patient was solely treated with intravenous diazepam, phenytoin bolus loading, isosorbide mononitrate sustained-release tablets, and bisoprolol tablets during this hospital stay, aside from VPA and warfarin. There are no acknowledged or identified interactions between warfarin and these drugs that are clinically significant in the literature or drug interaction database [4, 5]. Crucially, no other drugs, specifically antibiotics, proton pump inhibitors,

or vasoactive drugs, were given right before or during the hospital stay.

The two racemic active forms of warfarin are R-isomer (R-enantiomers) and S-isomer (S-enantiomers), as hepatic enzymes play a major role in their metabolism and serum depletion. It is important to note that the substances that induce or inhibit these enzymes can have an impact on how warfarin is metabolized and subsequently affect its concentration in the blood. Similarly, VPA acts as an inhibitor for CYP2C9, glucuronosyltransferase and epoxide hydrolase resulting in reduced deactivation of S warfarin and consequently leading to increased levels of this form in the bloodstream [5, 6]. It is worth mentioning that typically the influence of CYP inhibitors on warfarin metabolism begins within 24 hours after adding the inhibitor. The exact time it takes to reach maximal effect depends on when both interacting drugs reach their steady state [5, 6].

Another explanation refers to the role of VPA, which can occupy protein binding sites and cause an increase in Warfarin concentration in free or unbound form, especially since at therapeutic dosages, warfarin is more than 95% protein bound. This phenomenon can result in an elevated INR and eventually lead to an increased risk of bleeding [7]. In other cases, it has been demonstrated that VPA increases mean blood cell hemoglobin concentration, prolongs thrombin time, and dramatically lowers platelet count [8, 9].

The use of warfarin or anticoagulant drugs in patients with recurrent stroke can increase the risk of coagulopathy with signs of a mild to severe bleeding. There is a risk of complications in the form of intracranial hemorrhage with an INR index > 3 because the drug has a narrow therapeutic index making it difficult to titrate appropriately. The most common locations of bleeding are supratentorial and intraparenchymal [10]. In another report, warfarin use was also associated with hematoma expansion within 24 hours. Rapid correction of INR is likely to limit hematoma expansion. Older agents such as Vitamin K and fresh-frozen plasma are effective in INR correction but take hours to achieve complete INR correction [11, 12].

CONCLUSION

There are not many case reports describing interaction between the frequently prescribed medications, such as warfarin and divalproex sodium. Therefore, we report a case of significant subconjunctival bleeding and high INR with the concomitant use of valproic acid and warfarin.

Disclosure Summary: *The authors declare no conflict of interest, financial or otherwise, in this manuscript. Verbal informed consent has been obtained. No identification of the patient can be revealed.*

REFERENCES

1. Yoon HW, Giraldo EA, Wijdicks EF. Valproic acid and warfarin: an underrecognized drug interaction. Neurocrit Care. 2011 Aug; 15(1):182-5. doi: 10.1007/s12028-011-9544-5.
2. Zhou C, Sui Y, Zhao W, et al. The critical interaction between valproate sodium and warfarin: case report and review. BMC Pharmacol Toxicol. 2018 Oct 1; 19(1):60. doi: 10.1186/s40360-018-0251-0.
3. Anderson SL, Marrs JC. Probable Interaction Between Warfarin and Divalproex Sodium. J Pharm Technol. 2014 Feb; 30(1):8-12. doi: 10.1177/8755122513514379. Epub 2013 Nov 22.
4. Bruun E, Virta LJ, Kalviainen R, et al. Co-morbidity and clinically significant interactions between antiepileptic drugs and other drugs in elderly patients with newly diagnosed epilepsy. Epilepsy Behav. 2017; 73:71–76. doi: 10.1016/j.yebeh.2017.05.022.
5. Patsalos PN, Perucca E. Clinically important drug interactions in epilepsy: general features and interactions between antiepileptic drugs. LancetNeurol. 2003; 2(6):347-356. doi: 10.1016/S1474-4422(03)00409-5.
6. Cun-Li Wang, Victor Chien-Chia Wu, Kuo-Hsuan Chang, et al. Assessing major bleeding risk in atrial fibrillation patients concurrently taking non-vitamin K antagonist oral anticoagulants and antiepileptic drugs, European Heart Journal - Cardiovascular Pharmacotherapy, May 2020, 6 (3): 147-154.
7. Kouchaki B, Salehifar E, Janbabai G, et al. Major Interaction between Warfarin and Na Valproate: A Case Report. J Pharm Care 2014; 2 (4): 183-185.
8. Robertson P Jr, Hellriegel ET. Clinical pharmacokinetic profile of modafinil. Clin Pharmacokinet 2003; 42:123-37.
9. Zeller JA, Schlesinger S, Runge U, et al. Influence of valproate monotherapy on platelet activation and hematologic values. Epilepsia 1999; 40: 186-9.
10. Jimenez-Ruiz A, Gutierrez-Castillo A, Ruiz-Sandoval JL. Fatal Intracranial Hemorrhage Associated with Oral Warfarin Use. Cureus. 2018 Nov 12; 10(11):e3571. doi:10.7759/cureus.3571.
11. Teo KC, Mahboobani NR, Lee R, et al. Warfarin associated intracerebral hemorrhage in Hong Kong Chinese. Neurol Res. 2014 Feb; 36(2):143-9. doi:10.1179/1743132813Y.0000000275. Epub 2013 Dec 6.
12. Morotti A, Goldstein, J. N. Anticoagulant-Associated Intracerebral Hemorrhage. Brain Hemorrhages. 2020, 1(1), 89-94. doi:10.1016/j.hest.2020.01.001