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Major Interaction between Warfarin and Na Valproate: A Case Report

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ABSTRACT

Abstract: Warfarin is the most commonly used oral anticoagulant drug in clinical practice with extreme inter and intra-individual variation in pharmacokinetic properties.
Na Valproate, a broad spectrum anticonvulsant agent, is best known for its enzyme inhibition properties and also displacement of protein binding sites. Interaction between Warfarin and psychotropic drugs including Valproate are important and perhaps under recognized. In this report, we present a 48 year old female patient with chief complaints of abdominal pain, tea-color urine, blurred vision and headache. She had been suffering from "migraine headache" for 15 years that was relatively well controlled with Na Valproate 200mg twice daily. She was experienced a deep vein thrombosis (DVT) following oral contraceptive. For management of DVT, she was received Warfarin 5mg/day which was increased to 7.5 mg /day after 2 weeks. Three days after this increment of dose, her Prothrombin Time (PT) rose to 35.3 seconds (three times of normal value) and evidences of bleeding including hematuria and hematemesis were observed. Based on the history and laboratory findings, "Warfarin toxicity" was the first impression and she was treated with fresh frozen plasma and vitamin K with a well recovery. This experience emphasizes the clinical significant interaction between Warfarin and Na Valproate, which may take place even with the usual doses of each agent.

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Introduction

Warfarin is the most commonly used oral anticoagulant drug in clinical practice. It is a typical drug with narrow therapeutic window with a large number of drug interactions (1). Also, inter and intra individual variation in pharmacokinetic properties of Warfarin have been reported necessitating its close monitoring for ensuring safe and effective usage (2,3).

According to reports received by WHO between the years 1990 to 2010, Warfarin was among the most important drugs which was subject for various drug interaction both through pharmacokinetic and pharmacodynamics pathways (4). These reports also indicate that through these years Warfarin was the most prevalent drug that caused an ADR through a pharmacokinetic mechanism and second most prevalent with respect to pharmacodynamic mechanisms (4).

Na Valproate is an anticonvulsant drug with broad spectrum of activity on different kinds of seizure disorders. It is also useful in management of mood disorders and migraine headache prophylaxis. Like many other conventional anticonvulsant drugs, it has clinically significant interaction with commonly prescribed medicines (5). Na Valproate was also the fourth most common drug that produced an ADR by means of pharmacokinetic mechanisms (4). Valproate is best known for its enzyme inhibition properties but another

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pharmacokinetic mechanism that could potentially cause interaction is displacement of protein binding sites, which may not be sufficiently considered (6). The subject would be more complicated if notice that the metabolites of Valproate can also displace ligands from the Warfarin binding site (7). In co-administration of Valproate and Warfarin, this mechanism of interaction could result in rapid increase in INR which in turn could lead into dangerous clinical results (6). Although the presence of an interaction between Valproate and Warfarin have been postulated ago, the importance may be neglected in our practice (8-10). In this report, we present a clinically significant drug interaction between Warfarin and Na Valproate which was settled in usual doses of each agent.

Case Report

A 48 year old female patient was referred to Emam Hospital, an educational referral cenetr in Sari, Mazandaran Province, Iran, with chief complaints of abdominal pain and tea-color urine. At the time of admission, blurred vision and headache were other symptoms she reported. She also gave a history of observing blood in respiratory secretions in recent days. Her abdominal pain had a sustained and non-radiating entity and was also progressive during previous days. She denied any nausea or vomiting. Evaluating her past medical history revealed that she was suffering from "migraine headaches" for 15 years which was relatively well controlled with Na Valproate 200mg twice daily. Her previous admission was about 1 month ago because of a deep vein thrombosis (DVT) happened 3 weeks after initiating oral contraceptive (OCP). On that admission, she was discharged with Warfarin 5mg/day, which was increased to 7.5 mg /day two weeks later. Three days after this increment in dose, her PT rose to 35 seconds (a level of about three times greater than normal value). In the following days her symptoms appeared and finally when she came for an outpatient visit, her PT and INR were 36.7sec and 8.3 respectively. At this time, evidence of bleeding were present as her urine analysis showed presence of 2+ hematuria and 28-30 RBC/HPF, although she was relatively stable hemodynamicallyns. Her vital signs measurement was as following: blood pressure 100/70 mmHg; heart rate 80bpm; respiratory rate 12 breath/min and temperature 36.9^{oC}.Other laboratory values at the time of admission were shown in Table 1.

Table 1. Hematology, hemostasis and other laboratory data of the patient at the time of admission.

Hematology	Variables
WBC	6600/mm^3
RBC	4.01*10^6/mm^3
Hemoglobin	9.3 g/dl
Hematocrit	30.2 %
MCV	75.3 fL
MCH	23.2 pg
MCHC	30.8 g/dl
Platelet	444000/mm^3
RDW	15.1 %
PDW	11.2 fL
ESR	41 mm/h
Hemostasis	
D-Dimer	0.2 mg/L
PT(patient)	>36.7 sec
PT(control)	12.5 sec
PT activity	<18.6 %
INR	>8.3
Other Lab data	
Cr	0.6 mg/dL
Urea	25 mg/dL
Blood sugar	108 mg/dL
Amylase	71 U/L
Sodium	143 mEq/L
Potassium	5.5 mEq/L
CRP	8 mg/L

CRP: C-Reactive Protein, Cr: Creatinin, ESR: Erythrocyte Sedimentation Rate, MCV: Mean Corpuscular Volume, MCH: Mean Corpuscular Hemoglobin, MCHC: Mean Corpuscular Hemoglobin Concentration, RDW: Red Blood Cell Distribution, PDW: Platelet Distribution Width, PT: Prothrombin Time, INR: International Normalized Ratio.

Based on the history and laboratory findings, "Warfarin toxicity" was the first impression and she was ordered for admission in hematology-oncology ward. Because of complaints of blurred vision and headache, ophthalmologic and neurologic consultation requested. She was also suspicious for having retroperitoneal bleeding but abdomino-pelvic sonography ruled out presence of blood in abdominal cavity. In her MRI, no evidence of cerebrovascular accident was seen. Her ophthalmologic condition was also evaluated as being normal. As a result, a supportive therapy until the time INR comes back to therapeutic value was the main plan for her management.

Because of hematuria and hematemesis, she was ordered for taking six units of FFP stat and then two units TDS. She also received vitamin K 1mg subcutaneously. INR of the patient were measured two times a day. Trends

Table 2. Changes in INR values of the patient after admission.

Time after admission	1th day morning	1th day evening	2nd day morning	2nd day evening	3rd day morning	3rd day evening
PT (patient)	36.7	>30	15	13.4	12.6	12
PT (control)	12.5	12	12	12	12	12
INR	>8.3	>6	1.5	1.2	1.1	1

PT: Prothrombin Time, INR: International Normalized Ratio.

in decreasing INR are shown in Table 2.

Considering the risk of thromboembolic events, on the fourth day of admission, Warfarin was started again with a dose of 5mg/day, and she was requested to come back to outpatient clinic for follow up.

Discussion

In this case, Warfarin administered while the patients was taking Na Valproate for several years ago. To discuss the probable mechanism of this major interaction, it should be considered that Warfarin has two isomers; S and R. The S form has five to six times more anticoagulant activity than the R form. S-isomer and R-isomer are metabolized in the liver via separate pathways. The S-isomer(more active form) is almost exclusively metabolized via cytochrome P450 (CYP) isoenzyme 2C9 whilst the R-isomer is metabolized by CYP3A4, CYP1A2 and CYP2C19.(11) On the other hand, Na Valproate is a well-known inhibitor of CYP 3A4, CYP 1A1 and CYP 2C19 but not CYP 2C9. So, it is notable that enzyme inhibition and increase in Warfarin concentration may not provide an acceptable complete explanation for the mechanism of drug interaction between Valproate and Warfarin. Another explanation refers to the role of Valproate in occupying protein binding site which in turn results in increased Warfarin concentration as free or unbound form. From this point of view, a little change in protein binding (PB) of Warfarin due to the presence of a drug with strong affinity to binding sites of Warfarin (for example changing PB from 99% to 96%) could potentially lead to several fold increase (in this example 4 times increase) in Warfarin unbound fraction. Such phenomena in turn results in increased risk of bleeding.

In our case, the patient was subject for an increment in dose of Warfarin from 5 mg/day to 7.5 mg/day. We can assume that when protein binding sites of Warfarin are occupied with Valproate, the Warfarin which enters the blood circulation will face with less available sites for binding and tends to remain unbound more than the time that there is no high affinity drug with respect to protein binding. In this status, a minor change in the administered dose of Warfarin (2.5 mg in mentioned case) could potentially result in unexpected increase in anticoagulant effect as in less than a few days, INR raised to values more than eight. After receiving a single dose of vitamin k 1mg stat, 6 units of FFP stat and then 2 units TDS, over anticoagulation status of the patients came back to normal and in the third day of admission, her INR was 1 and Warfarin started again for DVT prophylaxis. By means of these interventions, our patient was successfully treated as her INR came back to therapeutic value two days post admission without any squeal.

In Conclusion, this case emphasizes that the Warfarin-Valproate drug interaction really has significant clinical consequences. This experience recalls us that taking a precise drug history is very important before initiating Warfarin therapy. Adding Warfarin to drug regimen of a patient receiving a high protein binding drug (e.g., Na Valproate) may enhance the risk of bleeding. Another issue is that in the presence of a drug with high affinity to serum proteins, a minute increase in Warfarin dose could potentially translated to exaggerated increase in INR.

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