Probable Interaction Between Warfarin and Divalproex Sodium

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Abstract

Objective: A potential interaction between warfarin and divalproex sodium is described. **Case Summary:** A 65-year-old Arabic-speaking Egyptian woman chronically anticoagulated with warfarin for atrial fibrillation and a history of stroke presented to the anticoagulation clinic with an elevated international normalized ratio (INR) of 3.2. This was an increase of 1.4 over her previous INR of 1.8 only 9 days prior. Discussion with the patient's daughter revealed the addition of divalproex sodium (a derivative of valproic acid) 250 mg twice daily to the patient's medication regimen 6 days prior. Other contributing factors that could cause an elevated INR were ruled out. The patient's total weekly dose (TWD) of warfarin was decreased from 22.5 mg to 20 mg, and the patient was instructed to return for a repeat INR in 1 week. On the day the patient was due to return for a repeat INR, she was admitted to the hospital and her INR was 2.2 on admission. Based on medication reconciliation information, the patient had decreased her warfarin TWD as instructed and had self-discontinued the divalproex sodium due to intolerable fatigue. During this time, the patient received no additional divalproex sodium. She was instructed to resume her previous TWD of warfarin of 22.5 mg on discharge and subsequently had a therapeutic INR (2.6) 11 days later. **Discussion:** Warfarin and divalproex sodium are commonly prescribed agents with few case reports to describe their interaction. Primary literature supports a multifactorial mechanism, including CYP450 metabolism inhibition and protein-binding displacement, both of which can result in an elevated INR. Use of the Drug Interaction Probability Scale indicated a probable interaction between warfarin and divalproex sodium. **Conclusions:** Patients receiving concurrent warfarin and divalproex sodium therapy should be monitored closely for changes in INR values as the combination may increase the INR and put the patient at increased risk for bleeding.

Keywords

anticoagulation, drug interaction, warfarin, divalproex sodium, cytochrome P450, protein binding

Warfarin is the most commonly used oral anticoagulant worldwide and, until recent years, the only such oral agent available.¹ Despite its effectiveness and ubiquitous use in patients with thromboembolic disorders, warfarin therapy is fraught with disadvantages including the need for frequent monitoring, a narrow therapeutic index, and a large number of clinically relevant drug–drug, drug–food, and drug–herb interactions. One such drug–drug interaction exists with valproic acid, another commonly prescribed medication for a variety of indications, but few case reports have described this interaction.^{2–4} We report the case of a patient chronically anticoagulated with warfarin who had a supratherapeutic international normalized ratio (INR) following the recent addition of divalproex sodium, a valproic acid derivative, to her medication regimen.

Case Report

A 65-year-old retired Arabic-speaking Egyptian woman (height 153.6 cm; weight 85 kg) chronically anticoagulated with warfarin for a history of stroke and atrial fibrillation

(CHADS₂ score = 3) presented to the anticoagulation clinic for her routine INR. The patient was taking 5 mg Sunday and Wednesday with 2.5 mg all other days of the week for a total weekly dose (TWD) of warfarin of 22.5 mg with a goal INR of 2 to 3. In addition to her anticoagulation indications, the patient's medical history also included type 2 diabetes mellitus, hyperlipidemia, chronic hematuria (since 2009), hypertension, goiter, constipation, depression, and headaches. In addition to warfarin, her drug therapy regimen included amitriptyline 12.5 mg daily, irbesartan 150 mg daily, botulinum toxin type A 100 units intramuscularly

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Table 1. Total Weekly Dosages of Warfarin and Corresponding Laboratory Test Results Over a 3-Month Period.

TWD Warfarin (mg)	INR	PT (seconds)	Days Since Last INR
22.5 mg	2.33	25.5	9
22.5 mg	2.13	23.8	7
22.5 mg	2.84	29.7	19
22.5 mg	3.28 ^a	33.2	11
20.0 mg	2.03	22.9	7
22.5 mg	1.77	20.6	5 ^b
22.5 mg	3.19	32.5	9 ^c
20.0 mg	2.18	24.2	7 ^{d,e}
	2.32	25.4	1 ^{d,e}
	2.24	24.7	1 ^{d,e}
22.5 mg	2.62	27.9	11 ^e

Abbreviations: TWD, total weekly dosage; INR, international normalized ratio; PT, prothrombin time.

^aINR elevation attributed to diarrhea and decreased oral intake.

^bPatient was to return in 7 days, but returned 2 days early. INR check on this date did not reflect the additional 2.5 mg added at the previous appointment.

^cPatient began taking divalproex sodium tablets 250 mg PO twice daily 6 days prior to this INR.

^dPatient was admitted to the hospital for acute dyspnea during the times these INRs were drawn. She received warfarin 2.5 mg PO daily during her hospitalization and was discharged home on TWD = 22.5 mg.

^ePatient was not taking divalproex sodium (self-discontinued due to extreme fatigue).

every 3 months, multivitamin (Centrum) daily, bisacodyl 10 mg prn, docusate sodium 100 mg twice daily, digoxin 125 µg daily, metformin 1000 mg twice daily, calcium carbonate/vitamin D₃ 500 mg/400 IU twice daily, paroxetine 40 mg daily, and simvastatin 20 mg daily. These medications at present doses had been stable for the previous 2 months.

The patient was adherent to follow-up with the anticoagulation clinic and often presented to the clinic more frequently than recommended due to her family wanting to ensure her INR was therapeutic. The patient lives with her daughter, who administers her medications and serves as her translator. The patient's INR values had been consistently therapeutic (INR 2.1-2.8) for the past 6 months on the TWD = 22.5 mg regimen with 2 exceptions: one slightly supratherapeutic INR that was attributed to decreased oral intake (patient had reported skipping meals) and one subtherapeutic INR that was expected and occurred during warfarin interruption and low-molecular-weight heparin bridging for a procedure. On the date of presentation, a Wednesday, the patient's INR was 3.2. While not critically supratherapeutic at 3.2, only 9 days earlier her INR had been 1.8 (Table 1, Figure 1), which is a change in INR of 1.4. The patient's daughter denied any changes to the patient's dietary intake and confirmed adherence with the patient's warfarin dosing, which she took each evening before bedtime. The daughter denied that the patient had recently experienced any vomiting or diarrhea. On further discussion, it was discovered that 6 days prior a neurologist initiated the patient on divalproex sodium tablets 250 mg twice daily for headache prophylaxis. This drug was not listed on her most recent medication list; however, it was noted in the neurology encounter in the patient's chart. The

patient denied any signs or symptoms of bleeding. The patient was instructed to decrease her warfarin dose to 5 mg on Wednesday and 2.5 mg all other days of the week (TWD = 20 mg) and to follow-up in 7 days for a repeat INR.

The day prior to her scheduled appointment for a repeat INR (6 days after her supratherapeutic INR), the patient's family had contacted her primary care provider's (PCP) office via telephone and left a message to inform him that the patient had discontinued her divalproex sodium due to a complaint of it causing extreme fatigue. The actual date of discontinuation is unknown. The PCP responded with a phone call to the patient and instructed her to resume divalproex sodium at a dose of 250 mg daily for 1 week after which she should increase the dose to 250 mg twice daily. The PCP discussed with the patient that divalproex sodium may initially cause fatigue.

The following day, the patient missed her appointment for her INR check as she was admitted to the hospital for acute dyspnea and was ultimately diagnosed with new heart failure with preserved ejection fraction. During her admission medication reconciliation, the patient confirmed discontinuation of the divalproex sodium and that she had not restarted it, despite the PCP conversation from the day prior. Pertinent vital signs on admission included blood pressure 163/107 mm Hg; heart rate 98 bpm; respiratory rate 16 breaths per minute; pulse oxygenation 93% on room air. Relevant laboratory values on admission included INR 2.18; prothrombin time (PT) 24.2 seconds; digoxin level 0.7 ng/mL (reference range = 0.7-2.1 ng/mL); D-dimer 0.14 µg/mL (normal <0.50 µg/mL); troponin <0.02 ng/mL (normal <0.03 ng/mL); N-terminal prohormone brain natriuretic peptide 2012 pg/mL (reference range = 0-125 pg/mL).

Figure 1. Timeline of divalproex initiation and discontinuation.

Liver function tests on hospital day 3, including albumin, were within normal limits. All INR values during her hospitalization were therapeutic (Table 1). The patient was given warfarin 2.5 mg daily on hospital days 1 through 4 and 5 mg on day 5. The patient was discharged during hospital day 6 and instructed to resume her previous dose of 5 mg on Sunday and Wednesday and 2.5 mg all other days (TWD = 22.5 mg). The patient received no doses of divalproex sodium, did not have a valproic acid level drawn during her hospitalization, and was not discharged home on this medication.

The patient returned for a posthospital discharge INR 8 days after discharge (11 days after her previous INR) and it was found to be 2.6. The patient's daughter confirmed that the patient had been taking TWD = 22.5 mg as instructed at hospital discharge with no missed doses and she was continuing to hold her divalproex sodium. The patient was instructed to continue this dose as her INR was therapeutic and return in 14 days for her next INR.

The Drug Interaction Probability Scale deemed the interaction between warfarin and divalproex to be probable (calculated score of 6).⁵

Discussion

Warfarin and valproic acid are independently known for their drug interaction potential, but relatively little documented regarding their interaction(s) with each other.^{2-4,6-9} The 2 most likely mechanisms by which a warfarin–valproic acid interaction may occur includes cytochrome P450 (CYP) isoenzymes and protein-binding displacement. Valproic acid is known to inhibit several isoenzymes with a

preferential inhibition of CYP2C9, which is the isoenzyme responsible for metabolism of the more pharmacologically active S-enantiomer of warfarin.¹⁰⁻¹² Because of this, valproic acid has the potential to inhibit warfarin metabolism via inhibition of CYP2C9 leading to increased concentrations of warfarin in the plasma.

Both warfarin and valproic acid are highly protein-bound (predominantly to albumin); valproic acid is at least 90% protein-bound while warfarin protein binding is more extensive at 97% to 99%.^{3,6} Due to high molar concentrations, valproic acid displaces other drugs (eg, warfarin) from their protein-binding sites, but warfarin has not been shown to displace valproic acid.^{6,7} Because warfarin is extensively protein-bound and has a narrow therapeutic window, nominal increases in the free fraction can lead to supratherapeutic concentrations putting a patient at increased risk for bleeding.^{2,3,8} Independent of its interaction with warfarin, valproic acid may decrease platelet aggregation and increase thrombin time, which may add to a patient's bleeding risk.⁹

A confounder related to CYP2C9 metabolism of warfarin is genetic polymorphisms, for example, *CYP2C9**2 and *CYP2C9**3, in the allele. These polymorphisms lead to impaired hydroxylation of the S-enantiomer of warfarin, which in turn leads to decreased metabolism and increased warfarin effect (ie, increased INR).¹²⁻¹⁵ As much as 1% to 2% of the Caucasian population is homozygous (eg, *2/*2, *3*3) or hemizygous (*2/*3) for this polymorphism, but the frequency in other ethnicities is low.¹² There are very little genotyping data in Middle Eastern patients, and the data in a small number of Egyptian patients are mixed. Shahin et al found significant differences in weekly

warfarin doses between wild-type homozygotes ($N = 122$; dose = 40.3 ± 19.5 mg), variant heterozygotes ($N = 60$; dose = 31.7 ± 14.8 mg), and variant homozygotes ($N = 13$; dose = 32.0 ± 14.1 mg), $P = .0028$.¹³ El Din et al studied 46 Egyptian patients taking warfarin and found that those with the $*2/*2$ ($n = 2$) and $*1/*3$ haplotypes ($n = 2$) required a lower daily warfarin dose (5.25 ± 1.77 mg and 6 ± 2.12 mg, respectively) compared to wild-type patients (8.24 ± 1.55 mg), $P < .05$.¹⁴ The most recent study cohort of 50 Egyptian subjects demonstrated no significant differences in weekly warfarin requirements between patients with the *CYP2C9* $*1/*1$ (wild-type; $n = 43$) and the *CYP2C9* $*1/*3$ allele ($n = 7$). The weekly warfarin dose in those with *CYP2C9* $*1/*1$ was 41.58 ± 14.58 mg and in those with *CYP2C9* $*1/*3$ was 41.0 ± 18.7 ($P = .925$).¹⁵ In each of these studies it was noted that the most prevalent genotype is the wild-type (*CYP2C9* $*1/*1$). Our patient's *CYP2C9* genotype was unknown and is statistically most likely to be that of the wild-type based on the available data. However, even if she had a genetic polymorphism, the length of time she had been on a stable dose of warfarin with a therapeutic INR would have ruled this out as the cause for the sudden increase in her INR when she initiated divalproex.

Despite the length of time that both warfarin and valproic acid have been commercially available, there are few published case reports of their interaction potential with one another. Two of the 3 available cases describe patients on chronic warfarin therapy that had valproic acid added to their regimen while the third describes the opposite. The first case report describes a 68-year-old woman undergoing warfarin treatment for a deep vein thrombosis (DVT) who was initiated on valproic acid 250 mg twice daily for schizophrenia and schizoaffective disorder. Her INR increased from a stable range of 1.8 to 2.6 to 3.9 the day after the addition of valproic acid.² In the second report, a 71-year-old woman with glioblastoma multiforme receiving warfarin for a history of DVT presented with refractory partial complex seizures. She was given an intravenous load of valproic acid and her INR increased from 3.4 to a peak of 7.6.³ The third report describes a 42-year-old woman who was receiving divalproex chronically for her bipolar disorder and was initiated on warfarin following a mechanical mitral valve replacement. Her INR at baseline was 1.11 and increased to 6.54 over 4 days on a daily dose of 2.5 mg of warfarin. Warfarin was held for 2 days, and the INR elevation persisted. The divalproex dose was then held and reintroduced at 250 mg twice daily, and the patient was discharged with an INR of 1.73.⁴ In each case an intervention was made to decrease the INR and no clinically relevant bleeding ensued.

One of the potential reasons behind the scarcity of case reports describing this interaction is that the clinical manifestations of the interaction (ie, elevated INR) may be transient. As the concurrent use of the 2 drugs continues, hepatic

elimination of valproic acid increases to more efficiently clear the drug and a new steady state with lower plasma levels of valproic acid is achieved.^{6,16} While this transient drug displacement may indeed become clinically irrelevant as the body achieves a new steady state, there is variability in how much drug displacement occurs and how long it takes to reestablish a steady state. The other factors that are not accounted for are dose titrations and adherence to drug therapy. In the case of our patient, she was initiated on divalproex sodium at a dose of 250 mg twice daily for headache prophylaxis and self-discontinued it after several days due to a complaint of extreme fatigue. After self-discontinuing her divalproex our patient was instructed to reinstate it at a lower dose (250 mg daily) and titrate up to 250 mg twice daily. This situation highlights 2 potential issues that could delay the time to steady state and prolong the protein-binding interaction: dose titrations and nonadherence. Based on the prescribing information, divalproex sodium is initiated at this dose for migraine headache prophylaxis and can be titrated up to 1000 mg daily based on patient response.¹⁷ Depending on the frequency with which the divalproex sodium is titrated, its interaction with warfarin can be prolonged as it will take longer to achieve steady state and the patient may experience an elevated INR for a prolonged time period. Similarly, nonadherence to divalproex will increase the time to steady state and may result in a subtherapeutic INR if the warfarin dose has been decreased to account for the addition of divalproex sodium.

This patient case and interaction highlights the need to be vigilant regarding the potential for a drug-drug interaction between warfarin and divalproex sodium. As highlighted, dose titrations and nonadherence can swing the INR in opposite directions, resulting in supratherapeutic or subtherapeutic INR values. While this interaction may be transient in a patient receiving stable doses of divalproex sodium and warfarin, changes in the divalproex dose may precipitate changes to the INR that could result in unfavorable outcomes. Close monitoring of the INR (eg, weekly) is prudent when divalproex is being initiated or the dose titrated in a patient concurrently taking warfarin. Our patient was fortunate in that her INR prior to starting divalproex was only 1.8 and she experienced no bleeding. Any increase in INR could have put her at greater bleeding risk, especially if she had been at the high end of the therapeutic range prior to divalproex initiation.

Conclusions

A patient with a previously stable warfarin regimen experienced an increased INR after the addition of divalproex sodium to her regimen. When this drug combination is used, frequent INR monitoring should be performed as the warfarin dose may need to be adjusted to avoid potential complications associated with an out-of-range INR.

Declaration of Conflicting Interests

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