

Warfarin and phenytoin drug interaction with possible purple glove syndrome

Carolyn S. Hunter, Stephanie V. Phan

Department of Clinical and Administrative Pharmacy, University of Georgia College of Pharmacy, Georgia, United States

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ABSTRACT

Though the impact of phenytoin on warfarin has been reported to potentiate the anticoagulant effect or interact in a biphasic manner, the effect of phenytoin on warfarin appears to be unpredictable and dependent upon multiple factors. Additionally, purple glove syndrome has rarely been reported secondary to therapeutic doses of oral phenytoin. We report on the case of a patient who experienced international normalized ratio (INR) fluctuations upon initiation of warfarin and phenytoin concurrently and who subsequently required discontinuation of therapeutic-dose phenytoin secondary to possible purple glove syndrome.

Key words: Drug interaction, phenytoin, purple glove syndrome, warfarin

INTRODUCTION

Despite the approval of new anticoagulants within the past several years, warfarin continues to be commonly used. Thus, awareness of drug interactions involving warfarin continues to be relevant. The impact of phenytoin on warfarin has been reported previously in the literature to potentiate the anticoagulant effect or interact in a biphasic manner.^[1-3] In these case reports, phenytoin was generally added to patients stabilized on warfarin therapy. We report the case of a patient who experienced persistently subtherapeutic international normalized ratio (INR) during initiation of warfarin and phenytoin concurrently and possible development of purple glove syndrome (PGS) at a therapeutic phenytoin dose.

CASE REPORT

A 47-year-old female was admitted to the hospital for suicidal ideation with lacerations on wrists and complaints of leg swelling. Prior to this admission, she had been noncompliant with medications after being discharged from another inpatient facility 3 days previously. Her past medical history included recurrent deep vein thrombosis (DVT), seizure disorder, bipolar disorder, and cocaine dependence. Pertinent surgical history included a bowel resection.

The patient had a current DVT confirmed via venous Doppler ultrasound and was receiving treatment dose enoxaparin 60 mg subcutaneously every 12 hours. She was also initiated on warfarin on admission with the goal to discontinue enoxaparin once warfarin reached therapeutic INR of 2-3. Her baseline INR was 1.02 [Table 1]. Phenytoin 400 mg orally at bedtime was also initiated on admission. Additional

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Address for correspondence:

Stephanie V. Phan, 1000 Jefferson Street, Albany - 31701, Georgia, United States. E-mail: sphan@uga.edu

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medications the patient received while admitted included ciprofloxacin, metronidazole, atenolol, esomeprazole, mirtazapine, sertraline, fluoxetine, duloxetine, trazodone, tramadol, acetaminophen, and enoxaparin. The INR began trending up appropriately, however, returned to baseline after 3 days of warfarin therapy [Table 1]. Despite dose increases, the INR returned to and remained at baseline. Possible medication nonadherence was suggested. The patient reported consistency with diet, no diarrhoea or vomiting, and medication adherence. A therapeutic phenytoin level of 15.3 mcg/mL (albumin 3.6 g/dL) on day 9 of phenytoin therapy proved consistency with patient reports of medication compliance. After 5 days of warfarin 10 mg and continued dose increases, the INR increased from 0.98 to 1.49. On day 13, the patient developed tingling, numbness and blue discoloration in the hands. Phenytoin was subsequently discontinued and switched to levetiracetam due to suspected purple glove syndrome and elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and gamma-glutamyltranspeptidase (GGT). The INR increased to 3.37 and the warfarin dose was reduced to 10 mg orally daily. The patient was discharged on day 15 and was subsequently seen in the pharmacist-managed Coumadin Clinic. Her INR 8 days after discharge was 1.9 on warfarin 10 mg daily; however, she was lost to follow-up after her initial visit.

Table 1: INR and warfarin dosing schedule

Day	INR	Warfarin dose (mg)	Notes
0	-	10	
1	1.02	5	Phenytoin initiated at 400 mg orally once daily at bedtime
2	1.14	5	
3	-	7.5	
4	1.21	10	Consistent diet, no vomiting or diarrhea, medication adherence documented
5	1.01	10	
6	1.03	10	
7	0.97	10	
8	1.1	10	
9	0.98	15	Therapeutic phenytoin level of 15.3 mcg/mL (albumin 3.6 g/dL)
10	1.49	12.5	
11	2.28	12.5	
12	1.84	12.5	
13	2.4	12.5	Tingling, numbness, blue discoloration of the hands noted. Phenytoin discontinued due to potential adverse effects and levetiracetam initiated
14	3.37	10	Hands noted to be "better". Enoxaparin was discontinued
15	2.32	Pt discharged on warfarin 10 mg once daily	

Note: INR checked the morning, warfarin dose given at 4:00 pm.
INR=International normalized ratio

DISCUSSION

The patient was receiving warfarin 10 mg orally daily for recurrent deep vein thrombosis and phenytoin 400 mg orally at bedtime for seizure disorder. Her INR fluctuated until phenytoin was discontinued, when it became supratherapeutic. Upon review of the patient's other medications and potential interactions, a majority of interactions would have led to prolonged INR and increased bleeding risk rather than subtherapeutic INR. We assessed for other causes, such as dietary factors, medication nonadherence, and impact on drug absorption of the history of small bowel resection. These factors did not appear to be responsible for the patient's INR fluctuations based on INR trends.

Warfarin is thought to inhibit the metabolism of phenytoin though plasma phenytoin levels may not be affected.^[1] Alternatively, prothrombin time is thought to be prolonged when phenytoin is added to warfarin therapy due to potentiation of warfarin half-life by phenytoin.^[2] It has also been reported that interactions occur because warfarin and phenytoin share a common metabolic pathway, that variable effects depend on possible competitive protein binding (though actual binding sites on the protein may be different), cytochrome (CYP) induction, and intrinsic metabolizing capabilities of each drug.^[3] Some case reports have documented drug interactions with the concomitant use of warfarin and phenytoin that lead to fluctuations in INR and hemorrhages.^[2,3] According to one study, a 65-year-old man on long-term warfarin therapy following mechanical heart valve replacement and taking phenytoin for generalized seizures experienced fluctuations in therapy throughout treatment. His INR was subtherapeutic when taking concomitantly and supratherapeutic when phenytoin was discontinued.^[3] Our case similarly follows the case reported by Levine *et al.*, where the patient's prothrombin ratio increased, but then decreased with concurrent phenytoin therapy. The difference was that phenytoin was initiated after warfarin had already been initiated and established, and our patient started warfarin and phenytoin concurrently, therefore an initial "jump" in the INR may not have been seen as each drug was not yet at steady state plasma levels, therefore the possible biphasic interaction was not as pronounced. Levine *et al.* proposed that the biphasic interaction was due to phenytoin displacement of warfarin from albumin binding sites and/or inhibition of warfarin metabolism, followed subsequently by phenytoin induction of CYP enzyme.^[2] Overall, the effect of phenytoin on warfarin appears to be unpredictable and dependent upon a multitude of factors.

We also reported that the patient's phenytoin, which remained at 400 mg nightly with no dosing changes, was switched to levetiracetam due to possible PGS and effects on liver enzymes. PGS is a rare dermatologic finding where the patient can present with bluish purple discoloration and edema at distal sites to cutaneous blisters, ulcers and sloughing of the

skin, if severe.^[4] Most case reports have documented PGS complications following intravenous (IV) administration of phenytoin; however, there are at least two case reports of possible PGS following oral phenytoin administration. One study was of a 10-year-old boy who was taking oral phenytoin 100 mg daily for a seizure disorder and was well controlled. However, the pharmacy mistakenly dispensed phenytoin 1000 mg daily and a few hours after the patient ingested the medication, he became drowsy and the mother noticed his hands and feet turned dark purple along with increased swelling. The mother discontinued the medication and took her son to the hospital. After 11 days of fluid therapy, his symptoms disappeared. This was thought to be the first report of PGS via oral administration.^[5] According to a more recent case report, a 35-year-old male presented with status epilepticus and received 1000 mg IV phenytoin in 100 mL of normal saline and lorazepam IV for seizure control. Once controlled, the patient was switched to oral phenytoin 300 mg daily. After 20 days of oral phenytoin therapy, the patient experienced pain and purple discoloration of hands that was not associated with any ulceration or elevated temperature. Upon consultation with dermatology, the phenytoin was switched to sodium valproate in divided doses, the patient's limbs were elevated and the patient was closely monitored. Over the next 10 days, the patient's signs and symptoms completely improved further supporting possible PGS. Although the authors conclude the patient experienced PGS on a therapeutic dose of phenytoin, the mechanism continues to remain unclear.^[6] Because phenytoin has known effects on liver enzymes and gamma-glutamyl transferase and due to the possible PGS despite oral, therapeutic-dose phenytoin, the medication was discontinued in favor of levetiracetam. The patient's symptoms did improve and, thereafter, the patient's INR became supratherapeutic and the warfarin dose required readjustment.

CONCLUSION

We present the case of a patient who experienced INR fluctuations upon initiation of all of her medications including warfarin and phenytoin. These INR fluctuations occurred until discontinuation of phenytoin due to possible and suspected PSG. Once the phenytoin was discontinued, the patient's PSG symptoms improved, although more rapidly than compared to the previously mentioned case reports. Though data on warfarin-phenytoin interactions and PSG development with oral doses of phenytoin are limited to case reports, our report contributes to existing information and is consistent with what has been previously reported.

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Conflicts of interest

There are no conflicts of interest.

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