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Managing the Drug-Drug Interaction With Apixaban and Primidone: A Case Report

Melanie M. Manis[1], Kat Petersen[1], Megan Z. Roberts[1], and Jeffrey A. Kyle[1]

Abstract

The management of the drug-drug interaction (DDI) between primidone, a moderate to strong cytochrome P-450 (CYP) 3A4 inducer, and apixaban, a direct oral anticoagulant (DOAC) and CYP3A4 substrate is complex and limited evidence exists to guide management. This case report describes a 65-year-old male, receiving primidone for essential tremor who developed an acute venous thromboembolism (VTE) requiring oral anticoagulation. DOACs are preferred over vitamin K antagonists for acute VTE treatment. Based on patient-specific variables, provider preference, and the avoidance of other DDIs, apixaban was selected. Apixaban's package insert recommends avoiding use with concomitant strong P-gp and CYP3A4 inducers due to the decreased exposure to apixaban; however, no recommendations are available for drugs that are moderate to strong CYP3A4 inducers and lack P-gp effects. Given that phenobarbital is an active metabolite of primidone, extrapolation of evidence from such literature is theoretical but provides insight into the management of this multi-faceted DDI. In the absence of the ability to monitor plasma apixaban levels, a management strategy of avoidance with a washout period of primidone based on pharmacokinetic parameters was used in this case. Additional evidence is needed to clearly understand the degree of impact and clinical significance of the DDI between apixaban and primidone.

Keywords
anticoagulants, drug-drug interactions, anticonvulsants

Introduction

Drug-drug interactions (DDI) with direct oral anticoagulants (DOACs; ie, apixaban, dabigatran, edoxaban, and rivaroxaban) are complex and mismanagement may lead to serious adverse events.[1] Due to the increasing prevalence of the use of DOACs as the preferred oral anticoagulant class for a variety of conditions, identification, and management of these DDIs is critical for ensuring patient safety and optimal outcomes.[2] The absorption and clearance of DOACs are influenced by varying degrees through the transporter permeability glycoprotein (P-gp) and the cytochrome P450 (CYP) isozymes. Concomitant drugs may inhibit or induce one or more of the enzymes and/or transporters. Inhibitors may increase exposure to the DOAC, while inducers may decrease exposure.[3] Enzyme induction and inhibition depends on a variety of factors such as the half-life of the drug, drug dose, rate of turnover of enzyme being impacted, and hepatic function. Given these interactions are influenced by a variety of factors and are not consistent among the DOAC class, a careful assessment of DDIs is required with individual DOACs and concomitant enzyme or transporter inducing or inhibiting agents.[3] Varying dose adjustments or avoidance are also required for individual DOACs in the presence of specific DDIs.[1,4-7]

Apixaban (20%-25%) and rivaroxaban (50%) are primarily metabolized by CYP3A4 but the other DOACs are not.[1,4,5] Edoxaban is the only DOAC not influenced in some degree by P-gp.[1,7] Several commonly prescribed medication classes, such as antiarrhythmics, antifungals, and anti-epileptic agents influence CYP450 enzymes and/or the P-gp transporter.[1] The Food and Drug Administration (FDA) recommends avoiding concurrent use of apixaban and rivaroxaban with strong dual inducers of CYP3A4 and P-gp (eg, rifampin, carbamazepine, and phenytoin) due to the reduction in plasma levels of apixaban and rivaroxaban.[4,5,8] No guidance is provided in the package insert for the management of DDIs with drugs that are moderate to strong CYP3A4 inducers

[1]Samford University McWhorter School of Pharmacy, Birmingham, AL, USA

Corresponding Author:
Melanie M. Manis, Samford University McWhorter School of Pharmacy, 800 Lakeshore Drive, Birmingham, AL 35229, USA.
Email: mmanis@samford.edu

and lack P-gp effects or vice versa.[4,5] Variability in classifying the degree (eg, strong vs moderate) of some enzyme-inducing drugs (EID) complicates the evaluation and management of these interactions. For example, primidone, a barbiturate used for seizure disorders and essential tremor, is listed by the FDA as a *moderate* 3A4 inducer, while Lexicomp® lists it is as a *strong* 3A4 inducer.[8-10] Furthermore, a paucity of data surrounding the impact of EIDs on concentrations of DOACs exists. Even less information is available regarding strategies to manage interactions with EIDs and DOACs. Case reports and retrospective studies describe stopping the EID, switching to warfarin, or monitoring DOAC concentrations as means for managing EID interactions with DOACs.[11]

This case report aims to describe the management of the DDI between apixaban and primidone in the setting of an acute venous thromboembolism (VTE). Primidone, is a moderate to strong inducer of CYP3A4 and its active metabolite, phenobarbital, is also an inducer of CYP3A4, and has a half-life of 50 to 150 hours.[8] Two case reports have described the management of the DDI with phenobarbital and apixaban,[12,13] but no data exists regarding the interaction with apixaban and primidone specifically.

Case Description

A 65-year-old, white male (BMI = 29.3 kg/m^2) with a past medical history of cryptococcal meningitis diagnosed 5 months prior, was admitted to the hospital reporting gait disturbance for 3 days. Additional pertinent past medical history included Parkinson's disease with tremor for which the patient took primidone 250 mg by mouth twice daily. Upon neurological exam, pertinent findings included a tremor on elevation of the right hand but not at rest, a mild right facial droop, and absent deep tendon reflexes at the ankles, knees, biceps, and triceps. As such, a lumbar puncture was performed and revealed a positive cryptococcal antigen and recrudescence of his cryptococcal meningitis. Intravenous (IV) liposomal amphotericin B and oral flucytosine were initiated. Renal and hepatic markers were within normal limits. On hospital day 5, he complained of left lower extremity pain and an ultrasound revealed a deep vein thrombosis (DVT) in the right superficial femoral vein and the right popliteal vein. Pharmacy was consulted to initiate apixaban by the primary physician, who also served as the patient's outpatient provider.

Upon review of concomitant medications, the pharmacist identified a significant DDI with apixaban and primidone that may result in reduced plasma concentrations of apixaban. The pharmacist recommended to avoid the drug combination given the inability to monitor plasma apixaban or anti-xa levels at the facility. The only alternative DOAC without this DDI is edoxaban, which was not covered by the patient's insurance, nor on hospital formulary.[7] A recommendation was made to initiate warfarin. However, given the patient's complex medical conditions the primary provider preferred to avoid warfarin. In the meantime, enoxaparin 1 mg/kg subcutaneous every 12 hours was initiated. Neurology was consulted to provide recommendations regarding the management of his essential tremor and parkinsonism. The neurologist implemented a rapid taper of primidone over 2 days, with close monitoring for worsening tremor. On hospital day 7, the patient received primidone 250 mg in the morning, 50 mg in the evening, and 50 mg twice daily on day 8. Primidone was discontinued indefinitely on day 9. Therapeutic enoxaparin continued for 17 days and apixaban 5 mg twice daily was initiated on day 23 of hospitalization, 14-days after primidone had been discontinued. On the day of apixaban initiation, his estimated creatinine clearance (CrCl) was 60 mL/min, hemoglobin was 12.7 mg/dL, and no updated liver enzymes were available.

Neurology signed off on hospital day 28, noting no worsening of tremor. On hospital day 40, the patient was transitioned from IV liposomal amphotericin B and oral flucytosine to IV fluconazole 800 mg daily due to a drug shortage of liposomal amphotericin B. On day 45, the patient was discharged to a rehabilitation facility on apixaban 5 mg twice daily and fluconazole 800 mg by mouth daily and there was no evidence of recurrent DVT, active bleeding or worsening tremor. Outpatient rehab notes were available 18 days post-discharge and did not contain documentation of worsening or recurrent DVT, nor signs and symptoms of bleeding. Pertinent medication adjustments are detailed in Figure 1.

Discussion

This case highlights the complexity of managing DDIs, which most often occur among patients receiving several medications for multiple comorbidities,[14,15] and the importance of interprofessional collaboration to optimize patient care outcomes. In this case, avoidance of the EID and DOAC was deemed the safest and most practical approach, given the paucity of evidence for clinical significance and management of the specific DDI between apixaban and primidone, along with the inability of the institution to measure plasma DOAC concentrations or oral factor Xa inhibitor specific anti-Xa levels. Discontinuation of the EID with enoxaparin transitioned to apixaban was feasible in this case.

The pharmacokinetics of the interaction with apixaban and primidone, including the half-life of 50 to 150 hours for the active metabolite, phenobarbital,[16] and enzyme turnover rates were taken into consideration. The timeframes for enzyme induction as compared to enzyme deinduction are vastly different and depend on unique variables. CYP450 enzyme induction is a slow process, and its kinetics are dependent on various factors including gene regulation events, mRNA and de novo enzyme synthesis, and systemic drug exposure. Enzyme induction times will significantly exceed the half life of the drug for these reasons and can take from 10 to 28 days or more.[17,18] Upon discontinuation of an

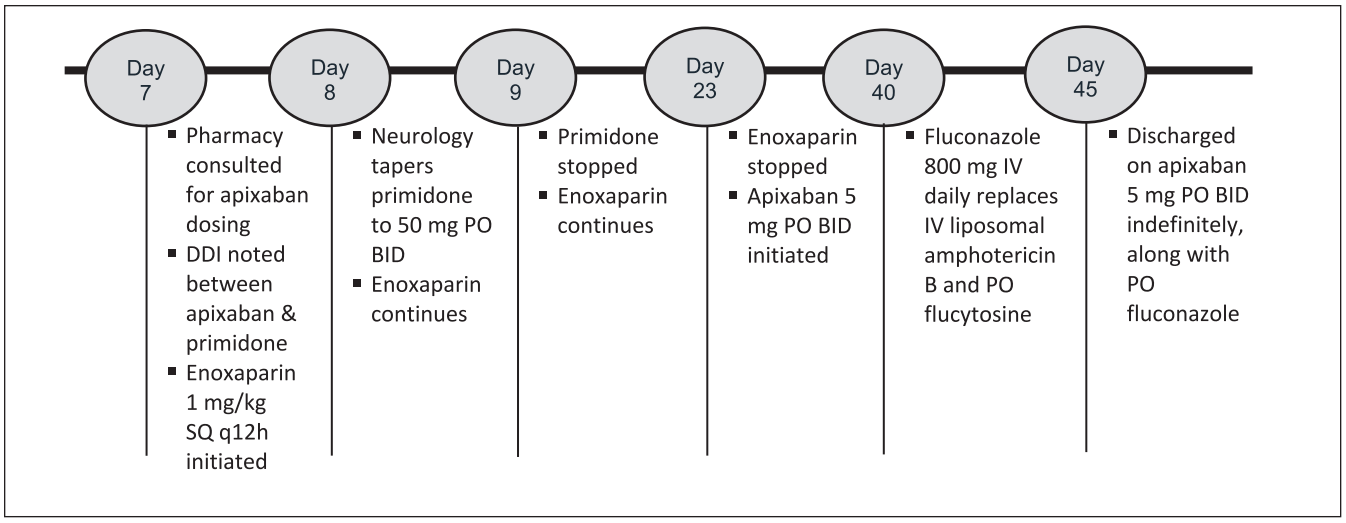

Figure 1. Timeline of drug-drug interaction management.

EID, enzyme deinduction begins with transcription levels returning to baseline in 18 to 24 hours. However, natural breakdown of the CYP450 enzymes is a first-order process and lags behind the decrease in enzyme synthesis and is dependent on the elimination of the EID and can take several weeks for return to baseline levels.[17] Given this information, the elimination of primidone and phenobarbital was estimated to occur between 10 and 30 days. The team selected 14 days as the time point at which enoxaparin would be transitioned to apixaban.

This approach is consistent with a case report describing the management of the phenobarbital and apixaban DDI in a patient with cardioembolic stroke. In this case, enoxaparin was administered for 8 weeks during a 6-week taper of phenobarbital. Apixaban was resumed 14 days after phenobarbital discontinuation.[13] A plasma phenobarbital concentration was undetectable at the time of transition to apixaban. Notably, a fourfold increase in plasma apixaban concentration (89-361 ng/mL) was reported after the taper and washout of phenobarbital.[13] Another case report describing management of the phenobarbital and apixaban DDI, details a concentration-guided approach where the patient remained on phenobarbital and plasma apixaban concentrations were obtained. Initial dosing of apixaban 2.5 mg twice daily for thromboprophylaxis due to atrial fibrillation required a dose increase to 5 mg twice daily to achieve plasma concentrations of apixaban consistent with those provided by the landmark Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study.[12,19] Despite advances in laboratory measurements of DOACs, it should be noted, no standard "therapeutic ranges" are available. Proper validation and verification of performance of laboratory assays is critical to ensure appropriate interpretation of DOAC concentrations in relation to expected trough levels for a given dose.[20] The 2021 Update of the International Council for Standardization in Haematology Recommendations for Laboratory Measurement of Direct Oral Anticoagulants provides expected plasma concentrations after therapeutic doses of individual DOACs. The guidelines specifically note that DDIs may be a nonurgent situation where DOAC concentrations may aid in determining over or underexposure of the drug, although more data is needed from larger cohorts.[21]

Retrospective observational studies provide additional insights into management of DOAC and EID DDIs.[11,22,23] Cohorts ranged from 17 to 32 patients, most frequently found to be receiving apixaban and carbamazepine (a strong CYP3A4 and P-gp inducer). Among patients in these cohorts who had plasma DOAC concentrations measured, plasma DOAC concentrations were lower than those in pivotal trials or provided reference ranges in 29 to 46% of patients. Perlman et al reported within their cohort (n = 22), DDIs were managed via discontinuation of DOAC or EID in 41% of patients and dose increase of DOAC in 14% of patients. No clinical outcomes data were reported.[11] The other cohorts reported increasing the DOAC dose or switching to an alternative oral anticoagulant, such as warfarin.[22,23] These retrospective studies support obtaining DOAC plasma concentrations when managing DOAC and EID DDIs; however, they do not include the specific DDI of apixaban and primidone. One additional retrospective study seeking to characterize DDIs of DOACs in hospitalized patients 65 years of age or older did identify a patient receiving primidone and a DOAC, but the specific DOAC and clinical outcome of this DDI were not specified.[24]

As mentioned previously, managing DOAC DDIs is complex and requires careful re-evaluation throughout the treatment course. Later in the patient's hospital course, another relevant DDI arose with the transition of antifungal therapy to fluconazole. Fluconazole is a moderate CYP3A4 inhibitor and thus the patient was at a potential increased risk of bleeding.[25] Prescribing information and drug-drug interaction

tools indicate that management of this DDI includes monitoring for adverse effects, including signs and symptoms of bleeding.[10,25] A symptomatic monitoring approach was utilized in this case due to lack of feasible alternatives for the patient's invasive fungal infection. Further considerations of the apixaban-fluconazole DDI are warranted as more evidence suggests a significant increase bleeding risk, particularly gastrointestinal bleeding.[26]

This case is the first describing the specific management of an apixaban and primidone DDI utilizing a washout period based on pharmacokinetic estimates of clearance and enzyme induction/deinduction and highlights interprofessional collaboration in DDI management. Further research is needed to understand the significance of this drug-drug interaction on clinical outcomes. Utilization of plasma DOAC levels would be beneficial to help determine clinical significance and guide management of future instances of apixaban and primidone interactions. More widespread availability of DOAC monitoring is warranted. In the meantime, research to determine management strategies when plasma DOAC concentrations are not attainable is imperative. Such ideas include monitoring EID plasma levels to confirm pharmacokinetic estimates of clearance, which may be more widely available.

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ORCID iD

Melanie M. Manis https://orcid.org/0000-0002-5850-6624

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