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Case Report

The Problem With Predictions: A Cautionary Tale of Empirically Adjusting Apixaban Dosing With Carbamazepine

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ABSTRACT

Concomitant use of apixaban and carbamazepine (CBZ) is not recommended due to an anticipated reduction in apixaban concentration, although few case reports describe this interaction. We report a case of initiating apixaban 10 mg twice daily (BID), in a patient stabilized on CBZ 600 mg BID that was guided by prior experience. Apixaban concentrations were substantially elevated with initial empiric dosing; apixaban dosing of 7.5 mg BID was eventually implemented. This case highlights the fact that the degree of induction by CBZ can vary, regardless of the dose, and requires clinicians to be cautious when applying prior experiences with patients to new patients.

RÉSUMÉ

L'utilisation concomitante de l'apixaban et de la carbamazépine (CBZ) n'est pas recommandée puisqu'on l'attribue à la réduction anticipée des concentrations de l'apixaban, bien que peu d'observations décrivent cette interaction. Nous présentons un cas sur l'amorce de l'apixaban (10 mg deux fois par jour [BID]) chez un patient stabilisé par CBZ, 600 mg BID (en fonction d'expériences antérieures). La posologie empirique initiale a fait substantiellement augmenter les concentrations d'apixaban; la posologie de l'apixaban de 7,5 mg BID a finalement été mise en place. Ce cas illustre le fait que le degré d'induction par CBZ peut varier, indépendamment de la dose, et obliger les cliniciens à être prudents lorsqu'ils transposent leurs expériences antérieures aux nouveaux patients.

Carbamazepine (CBZ) is a known strong inducer of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) and is to be "generally avoided" with apixaban, given that apixaban is a substrate for P-gp and is metabolized by CYP3A4.[1] Few case reports of this drug interaction exist; one showed no impact with concomitant apixaban 5 mg twice daily (BID) and CBZ 200 mg BID[2] whereas another required up-titration to apixaban 10 mg BID alongside CBZ 600 mg in the morning and 400 mg in the evening[3] to sustain apixaban trough/peak concentrations. Additionally, a different case report with concomitant apixaban 5 mg BID and CBZ 200 mg BID demonstrated relevant reductions in apixaban plasma concentrations, leading to a transient ischemic attack in a patient with atrial fibrillation.[4] Herein, we report a case of apixaban initiation that was guided by these prior case reports in a patient stabilized on CBZ 600 mg BID.

Case

A 39-year-old, 115-kg (body mass index: 46.1 kg/m^2) woman with complex cardiac disease taking CBZ therapy for long-standing epilepsy was admitted to her home hospital for tachycardia and COVID-19 pneumonia on May 7, 2021. Her past medical history included neonatal hypoxic brain injury post–cardiac surgery for complex congenital heart disease (Senning repair and transcatheter balloon atrial septostomy in 1982), cardiac arrest following a seizure, nystagmus, pacemaker implantation, and mild developmental delay (Fig. 1). She was transferred to a tertiary care facility owing to persistent tachycardia and low oxygen saturation but did not require intubation. She was treated with dexamethasone and tocilizumab (TCZ), and was empirically started on doxycycline and ceftriaxone, but the latter two (doxycyline and ceftriaxone) were discontinued.

Given her persistent and poorly tolerated intra-atrial reentrant tachycardia (atrial rate of 150 beats per minute) and persistent atrial fibrillation, she was initiated on

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Novel Teaching Points

- CBZ strongly induces CYP3A4 and P-gp, and a few case reports highlight a variable effect of CBZ on apixaban concentrations.
- Empiric administration of higher-than-normal doses of apixaban with concomitant use of CBZ should be done only in the setting of prompt assessment of apixaban concentrations, with an individualized assessment taking into consideration patient's thrombotic/bleeding risk and a review of all potentially interacting drugs.

enoxaparin 120 mg every 12 hours, on May 8 until May 12, 2021, planning for transesophageal echocardiography–guided cardioversion. Although she had a permanent pacemaker for antitachycardia pacing, the device was near the end of its battery life and would not deliver antitachycardia pacing. Therefore, amiodarone was initiated with a dose of 750 mg intravenously followed by 4000 mg orally divided over 5 days. Given her COVID-positive status, a point-of-care ultrasound was conducted instead of transesophageal echocardiography, and this revealed mildly decreased right ventricular systolic function with systolic bowing of the septum into the left ventricle, consistent with her new-onset heart failure symptoms.

When discussing options for this patient's anticoagulation therapy, neurology recommended against any change to her anti-epileptic medications, given that seizure control was optimal on long-standing doses of CBZ and lamotrigine. Warfarin was not initiated, as the patient had poor venous access and refused regular venipuncture draws required for warfarin monitoring. Thus, the anticoagulation management service was consulted to initiate apixaban.

Based on prior experience and her CBZ dose of 1200 mg/d, apixaban 10 mg BID (estimated glomerular filtration rate 105 mL/min) was initiated on May 12, 2021 (Table 1). Surrounding her 4th dose of apixaban, concentrations were drawn (trough 235 ng/mL; peak 457 ng/mL). Given these elevated concentrations, we held one apixaban dose and then decreased the dose to apixaban 5 mg BID.

Apixaban concentrations surrounding her 5th dose of apixaban 5 mg BID showed a trough of 37 ng/mL, and a peak of 209 ng/mL. Given the low trough, apixaban was increased to 6.25 mg BID on May 27. She was readmitted to her local hospital on May 31, 2021, with vomiting and atrial fibrillation. Her amiodarone dose was increased from 400 mg daily to 400 mg in the morning and 200 mg in the evening, while awaiting her pacemaker generator change. Apixaban concentrations drawn June 8 and reported 3 days later were within prior reference ranges (trough 126 ng/mL; peak 249 ng/mL), and apixaban 6.25 mg BID was continued.

She was admitted to a tertiary hospital from June 17 to June 23, 2021 (Fig. 1) for her generator change. Apixaban was held for 3 days prior to her procedure on June 17 (intended to be withheld 2 days, but the procedure was delayed 1 day) and restarted on June 18, 2021. Post-procedure, her amiodarone dose was reduced to 100 mg daily, as a higher heart rate was preferred to allow for pacing by the device.

Given the varying dosage and appreciating that the patient was not at steady state for amiodarone due to the short duration of therapy, we repeated measurement of apixaban concentrations 9 weeks post–hospital discharge, once she was medically stabilized in the community. Repeat concentration measures showed a trough on the lower end (46 ng/mL) and a peak of 168 ng/mL. With this finding, we elected to increase the apixaban to 7.5 mg BID. Before we planned for the next set of concentrations, we confirmed with the patient's electrophysiologist that the amiodarone dose was to remain stable (100 mg/d). Repeat concentrations evaluated 9.5 weeks later demonstrated a similar trough (43 ng/mL) and a higher peak (232 ng/mL). It was noted that this trough was drawn 15.5 hours post-dose. We elected to continue apixaban at 7.5 mg BID.

Discussion

Large clinical trials have shown that direct oral anticoagulants offer the advantage of fixed doses without the need for routine coagulation monitoring, compared with warfarin.

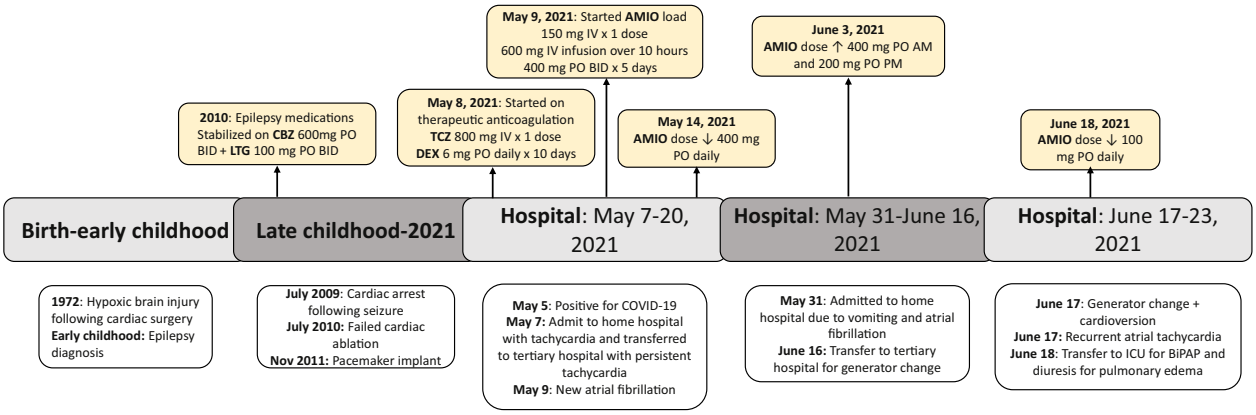

Figure 1. Case overview: patient's clinical course. AM, in the morning; AMIO, amiodarone; BID, twice daily; BiPAP, bilevel positive airway pressure (procedure); CBZ, carbamazepine; DEX, dexamethasone; ICU, intensive care unit; PM, in the evening; PO, by mouth; LTG, lamotrigine; TCZ, tocilizumab.

Table 1. Apixaban concentrations and subsequent changes in therapy

Apixaban concentrations		Apixaban concentration (ng/mL)* 103 (41,230)	171 (91,321)	
Date	Drugs	Trough†	Peak†	Change in therapy
May 12, 2021	Apixaban 10 mg BID initiated in the evening	235 Samples drawn: May 14 Concentrations reported: May 17	457	Held evening dose (May 17) ↓ apixaban to 5 mg BID (May 18)
May 18, 2021	Apixaban 5 mg BID	37 Samples drawn: May 20 Concentrations reported: May 25	209	↑ apixaban to 6.25 mg BID (May 27)
May 27, 2021	Apixaban 6.25 mg BID	126 Samples drawn: June 8 Concentrations reported: June 11	249	Continue apixaban 6.25 mg BID (June 11)
June 11, 2021	Apixaban 6.25 mg BID	46 Samples drawn: August 10 Concentrations reported: August 12	168	↑ apixaban to 7.5 mg BID (Aug 24)
Aug 24, 2021	Apixaban 7.5 mg BID	43 Samples drawn: October 14 Concentrations reported: October 19	232	Continue apixaban 7.5 mg BID

BID, twice daily.

*Based on apixaban 5 mg BID, as reported in the **A**pixaban for **R**eduction **i**n **St**roke and **O**ther **T**hromboembo**l**ic **E**vents in Atrial Fibrillation (ARISTOTLE) trial as median (5th, 95th percentile).

†Reference laboratory in Calgary, Alberta with the HemosIL Liquid Anti-Xa Assay (Werfen, Richmond Hill, ON) calibrated with the HemosIL Apixaban Calibrator.

However, as this case illustrates, the fixed-dose approach may not apply to all patients. Additional consideration may be required in cases in which a patient has drug-drug interactions, drug-disease interactions, and fluctuating renal function. Apixaban reference ranges have been reported based on sampling from randomized clinical trials; however, these are broad and not linked to clinical outcomes. Moreover, interpatient variability is reported to be approximately 30% for apixaban.[1] Given all these limitations, the assessment of apixaban concentrations is warranted in circumstances anticipated to substantially alter drug concentrations, such as drug interactions specific to induction of CYP3A4 and P-gp.

We initiated apixaban 10 mg BID based on a previous case report[3] that demonstrated the need to escalate apixaban to 10 mg BID in the setting of CBZ dose escalation to 600 mg in the morning and 400 mg in the evening (less than the current case's CBZ dose of 600 mg BID). Two case reports exist for patients on low-dose CBZ (200 mg BID)—one demonstrated reduced apixaban concentrations (undetectable trough; low peak of 29 ng/mL) leading to a transient ischemic attack,[4] and the other demonstrated little or no impact on apixaban concentration.[2] Given that we had experience with the latter case, we had inferred a CBZ dose—related induction of CYP3A4 and P-gp. Given the limited evidence of apixaban use with CBZ use, our assumption of a dose-related induction, and the need to balance the patient's thrombotic/bleeding risk with the ability to closely monitor the patient, we opted for a higher initial dose of apixaban. Apixaban concentrations were assessed around the 4th dose, while she was still an inpatient, as there was concern about ability to obtain these in her rural community. Her apixaban concentrations were much higher than we anticipated.

Our patient was prescribed other agents that may have impacted apixaban concentrations, specifically tocilizumab (TCZ) and amiodarone. TCZ is an anti-interleukin-6 (IL-6) receptor monoclonal antibody with a half-life of 13 days that is used in the treatment of various inflammatory conditions. Patients infected with COVID-19 may experience an elevation of IL-6 that decreases CYP3A4 mRNA by over 90%.[5] Given that TCZ blocks IL-6 receptor signaling, it can "normalize" CYP3A4 activity, thereby mitigating the impact of COVID-19 in reducing CYP3A4. Given this effect, the induction of CYP3A4 by CBZ could have been reduced, thereby contributing to elevated apixaban concentrations. Moreover, our patient was initiated on amiodarone within 1 week of our first set of apixaban concentrations, with loading doses and then differing amiodarone maintenance doses throughout the 4-month period of this case study. Amiodarone administered at maintenance dosing is expected to increase apixaban concentrations by 30%, given moderate CYP3A4 and P-gp inhibition, and no apixaban dose adjustment is recommended.[1] However, amiodarone does not reach the maximum influence of steady state for months. The limited data available in the literature are on maintenance therapy, reveal inconsistent results with respect to clinical outcomes, and did not include examination of apixaban

levels.[6,7] Therefore, we could postulate that the influence of amiodarone on apixaban levels would change throughout the time course of this study.

After the patient took apixaban 6.25 mg BID, repeated peak/trough assessments yielded apixaban concentrations that fell within clinical trial 5th and 95th percentiles, suggesting that our initial dosing of apixaban 10 mg BID was greater than that required to account for the CBZ interaction alone. The impact of COVID-19 and TCZ is speculative in our case. The impact of the initial amiodarone loading and higher ongoing maintenance dosing may have contributed to apixaban concentrations (drawn June 8), given the lower concentrations reported (August 10) following a reduction in amiodarone to 100 mg daily.

We note the following limitations in our assessment of apixaban drug concentrations. Amiodarone did not reach steady state, and the dose fluctuated throughout this patient's course, making assessment of apixaban concentrations difficult, as we were not certain of the impact of amiodarone. Additionally, the laboratory assay used to obtain apixaban concentrations was an indirect calculation using the degree of anti-Xa activity measured. In the clinical setting, this test was the most feasible option for assessing apixaban concentrations and allowed us to prioritize our patient's safety. However, in a research world, utilizing a liquid chromatography-mass spectrometry (LC-MS) assay would allow for direct measurement of the quantity of apixaban.

We report a case highlighting the importance of using caution in empirically adjusting apixaban doses based on anticipated cytochrome P450 and P-gp interactions. This case illustrates the unpredictable nature of drug-drug interactions with CYP3A4 enzyme induction/inhibition and highlights the variability in individual patient response. Patients such as this require additional consideration and management as other medications are added, or with the development of disease states such as decline in renal function. Additionally, periprocedural management of anticoagulation in patients whose therapy is clinically impacted by drug interactions requires additional planning, as standard approaches may not be appropriate. Given that there is no good way to quantify the impact of CBZ, we recommend both assessing each patient individually, without the inference of a dose-related enzyme induction by CBZ, and ensuring that clinicians perform a detailed review of all potentially interacting drugs. In doing so, upon balancing the patient's thrombotic/bleeding risk, we recommend implementing apixaban dosing with prompt assessment of apixaban concentrations to guide further dosing.

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