Case Report

Carbamazepine Induction Impacting Apixaban Concentrations: A Case Report

Tammy J. Bungard, BSP, PharmD,^a and R. Neil Roberts, MD^b

^a Division of Cardiology, University of Alberta, Edmonton, Alberta, Canada

^b Division of Neurology, University of Alberta, Edmonton, Alberta, Canada

ABSTRACT

Avoidance of apixaban with carbamazepine (CBZ) is recommended owing to an anticipated reduction in apixaban concentration, although this drug interaction is poorly described. We report a case wherein apixaban concentration was measured before and 2 weeks after CBZ. Apixaban concentrations were substantially reduced; hence, the dose of apixaban was doubled alongside a small increase in CBZ. Subsequent apixaban concentrations were essentially unchanged. This extent of reduction in apixaban concentration appears to be related to the dose of CBZ, with the interaction occurring over 2–4 weeks. This combination should be avoided unless apixaban concentrations can be assessed using a calibrated assay.

RÉSUMÉ

Il est recommandé d'éviter l'administration concomitante d'apixaban et de carbamazépine (CBZ) puisqu'il peut en résulter une baisse de la concentration d'apixaban. L'interaction médicamenteuse en cause est toutefois insuffisamment caractérisée. Un cas est décrit où la concentration d'apixaban a été mesurée avant l'administration de CBZ et deux semaines plus tard. La concentration d'apixaban ayant diminué considérablement, la dose d'apixaban a été doublée parallèlement à une légère augmentation de la dose de CBZ. La concentration d'apixaban n'a essentiellement pas changé à la suite de cette modification posologique. L'ampleur de cette réduction de la concentration d'apixaban semble liée à la dose de CBZ, l'interaction se produisant sur une période de 2 à 4 semaines. L'association des deux médicaments doit être évitée à moins que la concentration d'apixaban puisse être évaluée au moyen d'une méthode étalonnée.

Carbamazepine (CBZ) is a strong inducer of cytochrome P450 3A4 and P-glycoprotein (P-gp), whereas apixaban is primarily metabolized by CYP 3A4 and 3A5 and is a substrate for P-gp. Given this, “general avoidance” of the combination has been recommended with concern of a resultant reduction in apixaban concentrations.¹ We previously published a case report that demonstrated limited impact on apixaban concentration, although the CBZ dosing was low at 200 mg BID, leaving speculation as to whether the induction by CBZ may be dose related.² We present a case wherein CBZ was titrated upward with background apixaban therapy that demonstrates evidence of dose-related induction resulting in reduced apixaban concentrations.

Case Report

A 75-year-old man with nonvalvular atrial fibrillation (Congestive Heart Failure, Hypertension, Age, Diabetes,

Stroke/Transient Ischemic Attack [CHADS₂] = 3), hypertension, diabetes, and trigeminal neuralgia had been taking apixaban 5 mg BID since 2015, after refusal to continue to take warfarin. Up to 2015, he had taken CBZ 400 mg BID to control his pain attributed to trigeminal neuralgia, and this was discontinued when apixaban was started given the anticipated drug interaction. Despite numerous drug trials (baclofen, lamotrigine, pregabalin, and gabapentin), the patient reported severe pain intensity (7–10/10), described as sharp electrical shocks or jabs, that was aggravated by eating and washing/touching his face. A poor quality of life ensued, as he could not shave and continued to cancel dental appointments. As a result, in late 2018, CBZ was restarted. Given the wide reported reference ranges for apixaban concentrations, baseline concentrations before CBZ initiation were performed using an apixaban calibrated anti-Xa assay (Table 1). After 2 weeks of combined apixaban-CBZ therapy, substantial declines in both apixaban trough and peak concentrations (38% and 58% of baseline, respectively) were reported. In response, the dose of apixaban was increased to 10 mg BID. Notably, the patient had limited improvement in pain, so the CBZ was increased to 600 mg AM and 400 mg PM. Repeat apixaban peak and trough concentrations just over 2 weeks demonstrated concentrations that were essentially unchanged from the previous

Received for publication March 19, 2020. Accepted April 23, 2020.

Ethics Statement: This research adhered to relevant ethical guidelines.

Corresponding author: Dr. Tammy J. Bungard, 8425 Aberhart Centre, 11402 University Avenue, University of Alberta, Edmonton, Alberta T6G 2J3, Canada. Tel.: +1-780-407-8597; fax: +1-780-407-8907.

E-mail: tammy.bungard@ualberta.ca

See page 425 for disclosure information.

Novel Teaching Points

- Carbamazepine is a strong inducer of both cytochrome P450 3A4 and P-glycoprotein, and concomitant administration with apixaban is anticipated to reduce apixaban concentrations.
- Our case demonstrated a substantial reduction in apixaban concentrations that appeared to be related to the dose of carbamazepine and occurred over 2-4 weeks.
- This combination should be avoided unless apixaban concentrations can be assessed using a calibrated assay.

readings. The patient noted a lack of improvement in pain and reported CBZ-related side effects (increased drowsiness and nausea). Subsequently, approximately 1 month after administering CBZ 600 mg AM and 400 mg PM, dosage titration began, with the last dose being on February 13, 2019. Apixaban was reduced to 5 mg BID on February 11, 2019 (patient weight 84 kg; estimated glomerular filtration rate 80 mL/min). In April 2019, the patient had gamma knife radiosurgery performed and now reports a pain level of 3-4/10 with provocation (eg, rubbing his skin hard above his eyebrows).

Discussion

Our case demonstrates CBZ induction resulting in a substantial decline in apixaban concentrations, with concentrations falling well below baseline 2 weeks after CBZ initiation. Moreover, the subsequent doubling of the apixaban dose had little impact on subsequent trough/peak apixaban concentrations amid only a modest CBZ dose increase of 200 mg. There may be 3 explanations. First, the pharmacodynamic induction of CYP P450 3A4 and P-gp by CBZ may take longer than 2 weeks, and measuring apixaban concentrations at this time interval may not have yielded the

full impact of this induction. Second, it may be that induction by CBZ is dose related in a curvilinear fashion, with small CBZ dose increases resulting in a more substantial decline in apixaban concentrations. Third, indirectly measuring apixaban concentrations via a calibrated anti-Xa assay may have been insensitive to changes in concentration.³ A change may or may not have been detected had direct apixaban measurement by chromatography been available.

To manage this drug interaction, we initially assessed our patient's apixaban concentrations before starting CBZ. Although apixaban reference ranges are reported,¹ these are very broad and not linked to clinical outcomes, lending support for us to target concentrations similar to our patient's baseline. Our decision to assess apixaban concentrations approximately 2 weeks after concomitant apixaban-CBZ therapy was derived on the basis that our clinical experience demonstrated the warfarin-CBZ interaction results in international normalized ratio stabilization in 3-4 weeks. Given the prolonged pharmacodynamic effect of warfarin relative to apixaban, we reduced this interval to 2 weeks, anticipating that this was a conservative interval to identify changes in apixaban concentrations.

Given the titration off CBZ occurred over 3 weeks, the apixaban dose was left unchanged until close to the point of discontinuation of CBZ. This was done anticipating that the apixaban concentration would gradually increase over time (also taking 3-4 weeks), and we wanted to err on the side of ensuring adequate stroke prophylaxis for our patient. Although our case report was specific to induction by CBZ, it is notable that strong inhibitors or inducers of both CYP 3A4 and P-gp will impact apixaban concentrations.⁴

In summary, this case provides evidence of dose-related CBZ induction that imparts a reduction in apixaban concentration over a span of 2-4 weeks. Use of this combination should only be done with monitoring of apixaban concentrations, using an appropriately calibrated assay.

Table 1. Apixaban concentrations in relation to carbamazepine (CBZ) dosing

Date	Drugs	Apixaban concentration* (ng/mL)		Subsequent plan
		Trough [†]	Peak [‡]	
November 29, 2018	Apixaban 5 mg BID No CBZ	78	195	Start CBZ 400 mg CR BID [‡] (December 4, 2018)
December 17, 2018	Apixaban 5 mg BID CBZ 400 mg CR BID	30	114	Increase apixaban 10 mg BID (December 23, 2018) CBZ 34 µmol/L (December 17) Increase CBZ 600 mg AM and 400 mg PM (December 19, 2018) CBZ 36 µmol/L (December 29)
January 9, 2019	Apixaban 10 mg BID CBZ 600 mg AM and 400 mg PM	41	99	Taper CBZ 400 mg CR BID × 1 wk, then 200 mg BID × 1 wk, and 100 mg BID × 1 wk (finish February 13, 2019) Reduce apixaban 5 mg BID (February 11, 2019)

CR, controlled release.

* Reference laboratory in Hamilton, Ontario, with the STA-Liquid Anti-Xa Assay calibrated with the STA-Apixaban Calibrator (Diagnostics Stago, Asnières Sur Seine, France).

[†] Data reported from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial as median (5th, 95th percentile): Cmin: 103 (41, 230) ng/mL; Cmax: 171 (91, 321) ng/mL.¹

[‡] Target 25-50 µmol/L.

Funding Sources

No funding was received for this study.

Disclosures

T.J.B. has received unrestricted research grants from Leo Pharm and Pfizer, all unrelated to this manuscript. R.N.R. has nothing to disclose.

References

1. Eliquis Product Monograph. Kirkland, QC: Pfizer Canada; June 16, 2016.
2. Evanger N, Szkotak A, Stang L, Bungard TJ. Apixaban concentration with and without coadministration of carbamazepine: a case with no apparent interaction. *Can J Hosp Pharm* 2019;70:463-7.
3. Pollak PT, Mitchell LB. Monitoring direct oral anticoagulants: longing for the days when we were in control? *Can J Cardiol* 2019;35:694-8.
4. Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J* 2018;39:1330-93.