Institute of Pharmacology[1], Institute of Medical Biochemistry and Laboratory Diagnostics[2], Department of Nephrology[3], Department of Neurology and Centre of Clinical Neuroscience[4], First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic

Management of apixaban anticoagulation in a patient requiring therapeutic plasma exchange: a case report and a literature review

A. Pilková[1], J. M. Hartinger[1,*], I. Malíková[2], V. Satrapová[3], D. Šťastná[4], V. Tesař[3], O. Slanař[1]

Received May 5, 2024, accepted June 23, 2024

**Corresponding author: Jan Miroslav Hartinger, Institute of Pharmacology, First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic*
jan.hartinger@vfn.cz

Pharmazie 79: 159-162 (2024) *doi: 10.1691/ph.2024.4550*

Therapeutic plasma exchange (TPE) is used as an effective treatment modality for a variety of autoimmune disorders. Apart from its desired effect of removing pathological blood components, it also can remove coagulation factors and drugs. Currently, there is an insufficient amount of information regarding the use of direct oral anticoagulants in this setting. In this article, we present a case report of a patient with myasthenia gravis and chronic anticoagulation with apixaban who underwent a series of TPE while continuing apixaban treatment. We observed that only 10 % of daily dose was removed by the procedure and plasma levels of apixaban corresponded with expected range. TPE was not associated with shortened drug plasma half-life. We did not observe any significant alteration of apixaban pharmacokinetics during the period of TPE therapy, as well as no thrombotic or bleeding events. This case report supports the use of apixaban in patients treated by TPE, nevertheless, to firmly establish apixaban efficacy and safety profile in this clinical setting further research is needed.

1. Introduction

Managing chronic anticoagulation in patients requiring therapeutic plasma exchange (TPE) might be challenging, due to the fact that both plasma concentrations of an anticoagulant agent and coagulation factors may be influenced. Alterations in laboratory coagulation parameters (anti-Xa, aPTT, INR, antithrombin) have been described, particularly when albumin is used as a replacement fluid (Shunkwiler et al. 2028; Hodulik et al. 2019; Michalićková et al. 2022). Predicting the combined effects of anticoagulation and TPE is complicated. Especially with direct oral anticoagulants (DOACs), data on the effect of the procedure on drug exposure is limited and can be estimated from their pharmacokinetic properties only (Table 1). So far, only two case reports describing attempts to remove apixaban by TPE have been published with limited information regarding drug pharmacokinetics that do not allow drawing any serious conclusions (Lam et al. 2015; Francisco et al 2021). We present a case of a patient undergoing plasma exchange treatment while continuing chronic therapy with apixaban with extensive plasma concentration monitoring for safety/efficacy reasons. We also discuss our observation in the context of previously published case reports of DOAC treatment during TPE.

2. Case description

The 76-year-old patient (male, 171 cm, 76 kg) was admitted for newly developed dysphagia in a previously ocular form of myasthenia gravis. Due to the insufficient effect of corticotherapy (chronically 10 mg of prednisone per day, escalated gradually within nine days before admission to 30 mg per day), it was decided to perform TPE. In the past, the patient experienced two episodes of pulmonary embolism, for which he was chronically anticoagulated with apixaban at a dose of 5 mg twice daily. His concomitant medication consisted of pyridostigmine, prednisone, pantoprazole, ezetimibe and paracetamol (acetaminophen). Patient´s medical history included mild hepatic steatosis and chronic nephropathy with cysts of the right kidney, but at the time

Table 1: Pharmacokinetics of DOACs (Micromedex)

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Bioavailability	3-7 %	50 %	63.1 %	100 % with food
Protein binding	35 %	87 %	55 %	92-95 %
T_{max}	2 h	3-4 h	1-2 h	2-4 h
Vd	50-70 L	21 L	107 L	50 L
Clearance renal/non-renal	80/20 %	27/73 %	50/50 %	35/65 %
Elimination half-life	12-17 h 15-34.1 h (RI)	12 h 15.8 h (low body weight) 8.8. h (obesity) 14.6-17.6 (RI)	11.5 h	5-11.7 h 11-13 h (elderly) 8.7-9.5 (RI)
Dialysability	in part, with rebound effect	no	no	no

Abbreviations: RI – renal impairment; T_{max} – time to peak drug concentration; Vd – volume of distribution

Table 2: Apixaban drug monitoring in the course of TPE therapy

Day	TPE number	Anti-Xa (IU/mL)	Apixaban (ng/mL)	Time from previous dose (h)	Calculated $T_{1/2}$ (h) [Δ]	Time from the end of previous TPE (h)
0	-		108	15		
1	1	1.41	138	3	13.2	right before
		0.98	109	7.5		2.5
2	-					
3	2					
4	-					
5	3					
6	-	2.25	274	3	6.3	25
		1.55	167	7.5		29.5
7	4	2.44 (discharge) 2.52 (blood)	288[§] (discharge) 363 (blood)	3.5		right after
8	-	2.35	326	3		25
9	5					

[Δ] half-life was calculated according to formula T1/2 = ln(2)/[(ln(C1)-ln(C2))/Δt]
[§] further recalculated to 365 ng/mL (see the text)
$T_{1/2}$ - plasma half-life, TPE – therapeutic plasma exchange

of admission, laboratory findings were within normal range. Five consecutive centrifugal TPE sessions were provided on alternate days. Simultaneously, prednisone dose was increased to 40 mg per day and on day 5, azathioprine 25 mg per day was added to therapy with a plan to gradual increase the dose to a target dose of 50 mg twice daily. Apixaban was continued in the same dosing during the treatment with monitoring of plasma levels and coagulation parameters (incl. thrombin generation). Apixaban levels and timing of TPE sessions are listed in Table 2.

An apixaban level of 108 ng/mL was reported before admission to our hospital (day 0), approx. 15 hours after the last dose (the patient omitted one dose because of swallowing difficulty), the next two doses before the first TPE were administered via nasogastric tube (crushed). During the fourth TPE (day 7) apixaban level in the TPE discharge was measured to be 288 ng/mL (Table 2). As the discharge comprised not only from discharged plasma (2769 mL) but also from fluid used for flushing of the circuit, the final volume was 3508 mL and the calculated apixaban concentration in removed plasma before dilution was 365 ng/mL which is the same concentration as was in the plasma of the patient at the end of the TPE session. This makes the absolute amount of apixaban eliminated by TPE only approximately 1 mg, which is one tenth of daily dose and therefore is of minor clinical significance. The Figure depicts apixaban dosing during the hospitalization as well as timing of TPE sessions and apixaban plasma levels.

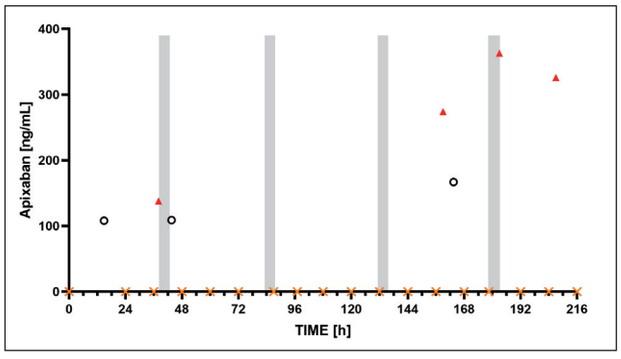

Fig.: Apixaban doses, levels and timing of TPE. Orange crosses – doses of apixaban (5 mg BID); grey bars – TPE; red triangles – plasma levels of apixaban 3-3.5 hours after administration; open circles – plasma levels drawn in different time

Thrombin generation (TG) was measured in plasma and TPE waste (Table 3). TG in patient´s plasma was influenced by apixaban exposure; and delayed thrombin peak, lower peak values and thrombin AUC were observed using both RCL and RCH assays (see Methods for details). This corresponds with values expected in patients anticoagulated by apixaban 5 mg twice daily. Measurement of TPE waste showed no measurable thrombin levels, probably due to lack of proteins necessary for its generation (Marlu et al. 2021).

The patient was dismissed on day 11 completely free of dysphagia, but on day 14, myasthenia gravis symptoms worsened again, with dysphagia and neck extensor muscle weakness. He was readmitted to the hospital and therapy with IVIG was introduced. During TPE therapy and until day 14, no signs of bleeding or thrombosis appeared.

3. Methods

Upon admission to the hospital, the patient signed informed consent forms wherein he agreed, *inter alia*, that his anonymous data could be used for research purposes including the publication of the research results. An approval for publication was obtained by the local ethical committee under the number 200/23 S. TPE with centrifugation was performed (Spectra Optia version 11, Terumo BCT) with citrate anticoagulation, 5 % albumin was used as a replacement fluid. Details of each procedure are described in Table 4. To monitor the effect of apixaban, we used the chromogenic assay of anti-FXa test with BIOPHEN® Heparin LRT (Hyphen Biomed, Neuville-sur-Oise, France) and anti-FXa calibrated assay using apixaban calibrator kit (Technoclone GmbH, Vienna, Austria). Monitoring of thrombin generation (TG) is based on monitoring the thrombin formation with a fluorogenic substrate using the Ceveron® Alpha analyzer (Technoclone GmbH, Vienna, Austria). TG in platelet-poor plasma was initiated using a recombinant human tissue factor (rhTF) in this assay. The maximum concentration of thrombin (peak thrombin in nM) generated and the endogenous thrombin potential (ETP; calculated from the area under the concentration – time curve (AUC)) were used for the analysis. TG analysis was performed using the assay kit for thrombophilia tendency testing Technothrombin® TGA RC Low (RCL) with a low concentration of phospholipid micelles containing approximately 5 pmol rhTF in Tris-Hepes-NaCl buffer and the anticoagulant activity assay kit Technothrombin® TGA RC High (RCH) with a high concentration of phospholipid micelles containing approximately 5 pmol rhTF in Tris-Hepes-NaCl buffer on an automated Ceveron® alpha analyzer with a TGA fluorometric module in accordance with the manufacturer's instructions.

Table 3: Fibrinogen and thrombin generation measurements

Day	TPE number	FBG (g/L)	FBG antigen (g/L)	TGA RCL tLag (min)	TGA RCL tPeak (min)	TGA RCL Peak (nM/L)	TGA RCL AUC (nM/L*min)	TGA RCH tLag (min)	TGA RCH tPeak (min)	TGA RCH Peak (nM/L)	TGA RCH AUC (nM/L*min)	time from previous apixaban dose (h)	time from the end of previous TPE (h)
6	-	1.33	1.14	3.7	17.5	38.4	925.5	4.5	12.8	68.5	986	3	25
		1.96	1.17	2.7	9.7	94.1	1436.7	3.7	8.9	139.6	1439.3	7.5	29.5
7	4	0.66*	0.77*	20.4*	23.8*	0*	0*	15.1*	26.9*	0*	0*	3.5	right after
		0.55	0.50	3.0	15.3	35.4	890.7	4.7	11.9	70.1	992		

* measurements in TPE discharge
AUC - thrombin area under the curve, FBG – fibrinogen, Ref. – reference range, TGA RCL - Technothrombin® TGA RC-low (RCL) (Technoclone GmbH, Vienna, Austria) with a low concentration of phospholipid micelles assay kit, TGA RCH – Technothrombin® TGA RC-high (RCH) (Technoclone GmbH, Vienna, Austria) with a high concentration of phospholipid micelles assay kit, tLag – thrombin generation time lag, tPeak – time to thrombin peak, TPE – therapeutic plasma exchange

Table 4: Characteristics of therapeutic plasma exchanges – details of individual procedures

TPE number/day of the treatment	1 / day 1	2 / day 3	3 / day 5	4 / day 7	5 / day 9
Weight (kg)	76.7	75.9	76.2	75.4	75.7
Exchange volume (ml)	2985	2990	3005	2769	2915
Duration of TPE (min)	135	136	133	165	121
Blood flow (ml/min)	40-60				

4. Discussion

This is the first case report focused on pharmacokinetics of repeated dosing of apixaban during TPE treatment. Due to the insufficient published data to guide apixaban therapy during TPE, several apixaban levels were measured in plasma as well as in the discharge. After the fourth TPE session, the concentration in the waste discharge fluid and plasma were similar and we quantified apixaban amount eliminated via TPE to be only 1 mg. This observed removal of apixaban represented 10% of the drug daily dose during TPE (that removes around 3 L of plasma) which is of minor clinical significance. The eliminated amount was consistent with the distribution characteristics of apixaban as it has a volume of distribution of ~ 21 L after an i. v. bolus (Byon et al. 2019). The decrease in apixaban concentrations during TPE did not exceed the decrease observed in the non-TPE period, as shown by the calculated $T_{1/2}$ values of 13.2 h vs. 6.3 h during the TPE procedure or outside it, respectively. When TPE was performed between dose administration and drug concentration measurement after 3 h, obtained plasma concentrations were not significantly different from concentration after non-TPE period. In the general population, median (5th to 95th percentile) C_{max} and C_{min} apixaban values obtained in clinical trials in patients with VTE are 132 (59-302) ng/ml and 63 (22-177) ng/ml, respectively (Byon et al 2017, 2019). In our case, C_{3h} levels were slightly above the expected values for a 5 mg BID dose. The only seemingly decreased C_{3h} concentration (138 ng/mL) was noted on the first day, prior to the first TPE, which was likely due to a previously omitted dose and possibly also the administration of previous two doses via nasogastric tube, which might not deliver the full amount of crushed drug. Laboratory monitoring of anticoagulant activity also indicated that despite TPE, the patient was adequately anticoagulated throughout the observation period.

To our best knowledge, there are currently only two case reports describing the use of apixaban in patients undergoing TPE. In both cases, TPE was provided with an intent to accelerate elimination of apixaban in patients with bleeding. Lam et al. (2015) reported a case of an 82-year-old patient with hemorrhagic pericardial effusion during apixaban treatment whose anti-Xa levels decreased from 0.76 to 0.22 IU/mL after TPE (calibrated for UFH) or 0.84 to 0.35 (calibrated for LMWH). Time between measurements was 8 hours, a 2-hour TPE with 3 L of fresh frozen plasma was provided at the end of this interval. Unfortunately, no drug concentrations have been obtained and anti-Xa levels not calibrated to apixaban have been shown to be highly unreliable for apixaban pharmacodynamic effect. Francisco et al. (2021) described a case of a 63-year-old female treated with apixaban, who underwent an emergent surgery for bowel obstruction, followed by bleeding. Two TPEs with plasma as replacement fluid were provided, during the first procedure, apixaban level dropped from 172 to 108 ng/mL, a day later after the second TPE, a level of 87 ng/mL was measured. However, such a decline in plasma concentrations could have been expected even without TPE and authors do not provide information about the apixaban level right before TPE nor the exact time interval between measurements which makes any reliable pharmacokinetic analysis impossible. Based on Lam´s case report or purely on theoretical assumptions some reviews on drug removal by TPE are suggesting effective apixaban removal (Mahmoud et al. 2021; Cheng et al, 2017) which is contrary to our findings.

Information regarding other xabans and the impact of TPE on their pharmacokinetics is sparse. Kumar et al. (2018) described probable rivaroxaban removal by TPE, which was provided to minimize risk of bleeding and allowing faster kidney transplantation to a 65-year-old male with ESRD, treated for atrial fibrillation with 20 mg rivaroxaban per day with the last dose being administered 12 hours before admission. After 90-min. TPE with replacement of 3 L fresh frozen plasma, anti-Xa dropped from 0.4 to 0.21 IU/mL (calibrated for LMWH), no rivaroxaban levels were provided. To our knowledge, there are no described case reports regarding edoxaban treatment and pharmacokinetics during TPE.

Two case reports described effect of TPE on dabigatran: Kamboj et al. (2012) described a patient of an unspecified age and renal functions, chronically treated with dabigatran, aspirin and intermittent NSAIDs use, who developed acute esophageal bleeding. After TPE, hemoglobin and hematocrit were stabilized but since the procedure was preceded with prothrombin complex administration and platelet transfusion and no data for either replacement fluid, dabigatran levels or coagulation tests after TPE were provided, an impact of TPE on dabigatran pharmacokinetics is hard to assess. Pflug and Schellinger (2020) described a case of a 76-year-old man receiving TPE for Guillain-Barré-Strohl syndrome. Chronically used dabigatran was withdrawn before the series of TPE, but unmeasurably high dabigatran level (>460 ng/mL) with bleeding and need for idarucizumab administration was noted after the second procedure. 24 hours after idarucizumab administration the rebound phenomenon occurred after the third TPE session (142 ng/mL) with subsequent small increase in dabigatran level after another 12 hours (163 ng/mL) requiring another dose of the antidote. Even after the second administration of idarucizumab followed by unmeasurable dabigatran level, laboratory finding during next days still indicated partial rebound of the drug presence in blood (32, 47, 39 and 29 ng/mL). A possible

state of overdose in a non-specified renal impairment might have contributed to excessive dabigatran body tissue stores in the case described by Pflug and Schellinger. These stores might have been mobilized after TPE and also an effect of TPE on idarucizumab cannot be ruled out although time between antidote administration and TPE exceeded 24 hours. The small increase in the dabigatran levels after the first measured rebound concentration suggests slow fading out of the antidote effect.

As with other information regarding drug removal during TPE (Mahmoud et al. 2021; Cheng et al. 2017; Ibrahim et al. 2012), also all these previously published case reports describe a situation of an overdose, sometimes with the use of other supportive measures. It is therefore impossible to draw conclusions from these findings regarding the therapeutic use of DOACs during TPE for patients with appropriate drug levels and no impairment of elimination functions.

5. Conclusion

DOACs theoretically represent relatively superior anticoagulants for patients undergoing TPE in comparison with UFH or LMWH, because their mechanism of action is independent of antithrombin levels that may be altered after TPE sessions. They also possess relatively larger volumes of distribution than parenteral anticoagulants which suggests a possibly smaller impact of plasma exchange on their anticoagulant effect. This is in line with our observations as we observed no alteration of apixaban pharmacokinetics during TPE treatment. Our findings are in contrast to the previous published case reports with apixaban and TPE that obviously have several methodological drawbacks. Since we performed thorough pharmacokinetic analysis of our data and we obtained plasma levels repeatedly to confirm our assumptions, we believe that our results are reliable. The treatment was effective and without complications which suggests that patients chronically treated with apixaban may continue in therapy during TPE. Nevertheless, more studies are needed for firm proof on efficacy-safety profile of DOACs in this setting.

Funding: MH CZ- DRO-VFN00064165

Acknowledgements: This work was supported by the Charles University project COOPERATIO (research areas Internal Disciplines, Pharmaceutical Sciences and Neurosciences).

Conflict of interest statement: The authors have no conflict of interest to declare.

References

Byon W, Garonzik S, Boyd RA, Frost CE (2019) Apixaban: A clinical pharmacokinetic and pharmacodynamic review. Clin Pharmacokinet 58: 1265–1279.

Byon W, Sweeney K, Frost C, Boyd RA (2017) Population pharmacokinetics, pharmacodynamics, and exploratory exposure-response analyses of apixaban in subjects treated for venous thromboembolism. CPT Pharmacometrics Syst Pharmacol 6: 340-349.

Cheng CW, Hendrickson JE, Tormey CA, Sidhu D (2017) Therapeutic plasma exchange and its impact on drug levels: An ACLPS critical review. Am J Clin Pathol 148: 190-198.

Francisco MT, Arana Yi C, Padrnos L, Braga S, Adamski J (2021) Therapeutic plasma exchange for apixaban removal in the setting of delayed clearance and life-threatening bleeding. Blood 138 (Suppl 1): 4271.

Hodulik KL, Root AG, Ledbetter LS, Onwuemene OA (2019) Effects of therapeutic plasma exchange on anticoagulants in patients receiving therapeutic anticoagulation: a systematic review. Transfusion 59: 1870–1879.

Ibrahim RB, Balogun RA (2012). Medications in patients treated with therapeutic plasma exchange: prescription dosage, timing, and drug overdose. Semin Dial 25: 176–189.

Kamboj J, Kottalgi M, Cirra VR, Shah N, Kamboj R (2012) Direct thrombin inhibitors: a case indicating benefit from 'plasmapheresis' in toxicity: a call for establishing "guidelines" in overdose and to find an "antidote"! Am J Ther 19: e182–185.

Kumar V, Allencherril J, Bracey A, Chen AJ, Lam WW (2018) Therapeutic plasma exchange for urgent rivaroxaban reversal. Tex Heart Inst J 45: 96–98.

Lam WW, Reyes MA, Seger JJ (2015) Plasma exchange for urgent apixaban reversal in a case of hemorrhagic tamponade after pacemaker implantation. Tex Heart Inst J 42: 377–380.

Mahmoud SH, Buhler J, Chu E, Chen SA, Human T (2021) Drug dosing in patients undergoing therapeutic plasma exchange. Neurocrit Care 34: 301-311.

Marlu R, Naciri Bennani H, Seyve L, Noble J, Chevallier E, Motte L, Imerzoukene F, Bugnazet M, Christophe M, Malvezzi P, Jouve T, Rostaing L (2021) Comparison of three modalities of plasmapheresis on coagulation: Centrifugal, single-membrane filtration, and double-filtration plasmapheresis. J Clin Apher 36: 408–419.

Michaličková D, Hartinger JM, Hladinová Z, Bednářová V, Szonowská B, Polakovič V, Matthios A, Tesař V, Slanař O, Krekels EHJ (2022) Population pharmacokinetics-pharmacodynamics of fondaparinux in dialysis-dependent chronic kidney disease patients undergoing chronic renal replacement therapy. Eur J Clin Pharmacol 78: 89–98.

Pflug MA, Schellinger PD (2020) Recurrent and drastic increase in dabigatran levels may be induced by therapeutic plasma exchange. J Stroke 22: 266–267.