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Recurrent venous thromboembolism in primary membranous nephropathy despite direct Xa inhibitor therapy

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Abstract

Clinically apparent venous thromboembolism (VTE) occurs in approximately 7% of patients with membranous nephropathy. Hypoalbuminemia at diagnosis is an independent risk factor for VTE, and risk increases significantly as albumin falls. Optimal prophylactic and treatment anticoagulation regimens in the nephrotic syndrome remain unproven but novel oral anti-coagulants have become attractive therapeutic options. We describe a patient diagnosed with anti-phospholipase A2 receptor antibody positive membranous nephropathy and recurrent VTE while on therapeutic dosing of apixaban. A direct factor Xa inhibitor, apixaban has been shown to be non-inferior to warfarin for the treatment of VTE in the general population. However, because it is highly protein-bound, apixaban may have altered pharmacokinetics and pharmacodynamics in patients with nephrotic syndrome and hypoalbuminemia. This case report highlights the need for further studies of direct oral anticoagulants to fully assess their effectiveness in this high-risk population.

Keywords

Glomerulonephritis; Membranous nephropathy; Venous thromboembolism/etiology; Serum albumin/analysis

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the individual participant whose case was reported.

Introduction

In the United States, membranous nephropathy has an incidence of 12 per million per year and 70–80% of patients exhibit IgG4 antibodies directed to the podocyte antigen phospholipase A2 receptor (PLA2R) [1, 2]. Clinically-apparent VTE is a life-threatening complication occurring in 7.2% of patients, and risk increases significantly with a serum albumin level below 2.8 g/dL [3]. Optimal prophylactic and treatment anticoagulation with direct oral anticoagulants (DOACs) in nephrotic syndrome remain unproven [4, 5]. Apixaban, a direct factor Xa inhibitor, is effective in the general population for VTE treatment, but has not been well studied in nephrotic syndrome. With its high protein binding, apixaban pharmacokinetics (PK) and pharmacodynamics (PD) may be altered by hypoalbuminemia. We present a patient with anti-PLA2R antibody-positive membranous nephropathy with recurrent VTE while taking appropriately dosed apixaban.

Case report

A healthy 51-year-old Caucasian male presented to his physician with new onset headache, bilateral lower extremity edema and blood pressure of 220/120 mmHg. Imaging demonstrated acute left popliteal deep vein thrombosis (DVT) extending into the femoral vein, external iliac vein and inferior vena cava (IVC). Chest computed tomography (CT) revealed bilateral pulmonary emboli including the right main pulmonary artery. Following infusion of intravenous unfractionated heparin, he underwent mechanical thrombectomy with 4 days of catheter-directed thrombolytics. Two iliac stents were placed due to iliac vein compression syndrome. For unclear reasons, he was discharged on reduced dose apixaban 2.5 mg twice daily.

Six weeks later, repeat ultrasonography showed old DVT with partial recanalization in the left common femoral and external iliac veins, and patent IVC. However, he quickly developed worsening bilateral lower extremity edema and scrotal swelling. CT venogram demonstrated new thrombus of the left external iliac, common femoral veins and the IVC, extending from below the renal veins into the intrahepatic IVC. His anticoagulation was switched to fondaparinux, and he was referred to hematology and vascular surgery at our institution.

Further studies revealed a serum albumin of 2.1 g/dL, urinalysis with 3+ protein, and urine protein-to-creatinine ratio (UPCR) of 13.0 g/g. Initial thrombophilia evaluation was negative for Antithrombin III and Protein C and S deficiencies though factor V Leiden and factor II mutation were not performed. He was admitted for repeat catheter-directed thrombolytics. Nephrology was consulted for nephrotic syndrome. Creatinine on admission was 0.88 mg/dL. Urine sediment revealed oval fat bodies and fatty casts. Total cholesterol was 301 mg/dL. ANA, HIV, Hepatitis B, Hepatitis C and RPR were negative; C3 and C4 complement were within normal limits. Hemoglobin A1c was 5.3%. Serum protein electrophoresis with immunofixation was negative for monoclonal protein. PLA2R antibody titers were pending at discharge. He received intravenous diuretics, an angiotensin II receptor blocker, and a statin. With the need for urgent anticoagulation and recent thrombolytics, renal biopsy was

deferred. Before discharge, he started apixaban 5 mg twice daily, as hematology felt the prior dosing was sub-therapeutic.

Two weeks later, serum albumin was 2.0 g/dL and spot UPCR remained elevated at 13.6 g/g. PLA2R antibody titers returned elevated to 424 RU/mL (reference value > 19 RU/ mL: Positive). Prostate specific antigen was 1.63 ng/mL (reference range 0–4.0 ng/mL), and colonoscopy was unremarkable. He was diagnosed with presumed idiopathic membranous nephropathy (iMN) and began a 6-month course of cyclical alternating monthly corticosteroids and oral cyclophosphamide. He remained on apixaban 5 mg twice daily.

After 5 months, the patient's blood pressure and edema improved, and UPCR decreased to 5.0 g/g. Repeat PLA2R antibody was undetectable at < 2 RU/mL, but serum albumin remained low (2.6 g/dL). Shortly thereafter, he developed worsening left leg swelling with elevated d-dimer to 2345 ng/mL (normal < 230 ng/mL). Doppler ultrasonography revealed new left mid femoral DVT, as well as acute on chronic proximal femoral left lower extremity DVT.

The patient and his spouse reported adherence to his apixaban and denied missing doses. However, a peak (4-h) apixaban total plasma concentration returned at 50.4 ng/ mL [predicted median maximal plasma concentration (C_{max}): 132 ng/mL (90% CI 125.2–139.3 ng/mL)] [6]. Due to recurrent thrombosis and sub-therapeutic C_{max}, despite appropriate dosing and self-reported adherence, apixaban was discontinued. After discussing options of warfarin vs low-molecular weight heparin or fondaparinux, the patient elected to restart fondaparinux.

One year from diagnosis, the patient had no further VTE and serum albumin improved to 3.3 g/dL. PLA2R remained negative and total cholesterol was 121 mg/dL. Proteinuria remained in the nephrotic range at 7.1 g/g. Anticoagulation was temporarily held for renal biopsy. Pathology revealed stage III membranous glomerulopathy with focal and segmental glomerular scarring, and mild tubulointerstital scarring. The patient was treated with intravenous rituximab (1 g followed by an additional 1 g 2 weeks later), and UPCR was 4.3 g/g at 21 months post-diagnosis. Although serum albumin remained above 3 g/dL, the patient was hesitant to stop anticoagulation and remained on fondaparinux.

Discussion

The utility of prophylactic anticoagulation in iMN has not been explored in randomized control trials. The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines suggest the consideration of warfarin therapy in patients with nephrotic syndrome when serum albumin is less than 2.5 g/dL, and with "additional risks for thrombosis" (graded 2C) [7]. Studies following the KDIGO guidelines demonstrated iMN has the highest risk of VTE compared to other glomerular diseases, and that the level of serum albumin at diagnosis is inversely related to risk [3, 8]. Ultimately, patients and providers together must weigh the level of bleeding risk against potential benefits of anticoagulation. An individualized decision analysis model on the risks and benefits of warfarin anticoagulation in patients with

membranous nephropathy with a risk calculator is available online (https://www.med.unc.edu/gntools/) [9].

Per KDIGO guidelines, no recommendations can be made regarding DOACs for VTE prophylaxis in nephrotic syndrome "due to insufficient experience" though recent case reports have demonstrated success [4, 7]. In the general population, DOACs are non-inferior to warfarin for VTE prophylaxis and have lower incidence of intracranial bleeding [10]. For those with CKD, rivaroxaban was superior to warfarin in preventing episodes of strokes (0 vs 25), DVT's (0 vs 5) and major bleeding (2 vs 8) as part of non-valvular atrial fibrillation management [11]. DOACs also lack dietary interactions, have a rapid onset of action, and do not require recurrent monitoring, making them an attractive choice to patient and provider. However, not all DOACs currently have FDA approved reversal agents and major GI bleeding may be an increased with dabigatran and rivaroxaban [10, 12, 13].

The PK/PD, safety, and efficacy of DOACs in the setting of hypoalbuminemia is also unclear. While only 35% of dabigatran (a direct thrombin inhibitor) is protein-bound, plasma protein binding of apixaban and rivaroxaban (direct factor Xa inhibitors) is greater than 85% (Table 1). Since the drug's unbound fraction is the pharmacologically active component, it has been previously hypothesized that a low protein state (such as in nephrotic syndrome) could lead to drug toxicity due to reduced binding sites [14]. Our patient's 4-h total apixaban concentration (both bound and unbound fractions) was measured using the liquid chromatography/tandem mass spectrometry (Labcorp, Burlington, NC, USA). Despite self-reported adherence to a 5 mg twice daily dosing regimen, the patient's estimated C_{max} returned lower than expected at 50.4 ng/mL. Based upon data from the AMPLIFY trial for venous thromboembolism treatment, the predicted median C_{max} for patients receiving a 5 mg BID dose was 132 ng/mL (90% CI 125.2–139.3 ng/ mL) [6]. Notably, the unbound fraction of drug is metabolized and subsequently eliminated while the protein-bound portion serves as a depot, slowly dissociating the drug to maintain equilibrium. Thus, the amount of plasma protein can also influence a drug's metabolism, clearance, and biological half-life. Given the patient's hypoalbuminemia, we posit an initial higher fraction of unbound drug was freely metabolized and excreted, accelerating the release of the bound fraction, and shortening the half-life. Ultimately, this may have resulted in a concentration below the threshold needed for thromboprophylaxis between his 12-h dosing interval that contributed to recurrent thrombus. Apixaban is O-demethylated and hydroxylated to inactive metabolites by the mixed function oxidase, cytochrome P450 3A4/5 (CPY3A4/5), and is transported across cell membranes by the P-glycoprotein (P-gp) multidrug transporter protein [15]. Drugs that affect the activity of CYP3A4/5 and P-gp can also potentially change the exposure, bleeding risk, and efficacy of apixaban. The patient was not prescribed any medications with dual CYP3A4 and P-gp inhibitor or inducer properties that would significantly alter the PK profile of apixaban.

Following his recurrent DVT, the patient was switched to fondaparinux, which he previously tolerated. Fondaparinux is a synthetic pentasaccharide factor Xa inhibitor administered as a once daily subcutaneous injection. Unlike direct factor Xa inhibitors but similar to heparin, fondaparinux mediates its effects indirectly through antithrombin III. Fondaparinux is highly and specifically bound to antithrombin III in human plasma, and importantly is not bound to

albumin. Due to its renal elimination, fondaparinux is contraindicated if creatinine clearance is < 30 mL/min [22]. This patient remained free of VTE after switching to fondaparinux, but his underlying disease also improved with a serum albumin above 3.0 g/dL. Whether his lack of further thrombotic events was due to the change in anticoagulation, or due to his improved nephrotic syndrome remains unclear.

As DOACs are more widely prescribed, caution should be exercised in their use for prophylaxis and treatment of VTEs in nephrotic patients until additional data is available. This case highlights the need to fully assess DOAC pharmacokinetics, pharmacodynamics, safety and effectiveness in this high-risk population.

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References

1. Cattran DC, Brenchley PE (2017) Membranous nephropathy: integrating basic science into improved clinical management. Kidney Int 91(3):566–574. 10.1016/j.kint.2016.09.048 [PubMed: 28065518]
2. De Vriese AS, Glassock RJ, Nath KA, Sethi S, Fervenza FC (2017) A proposal for a serology-based approach to membranous nephropathy. J Am Soc Nephrol 28(2):421–430. 10.1681/ASN.2016070776 [PubMed: 27777266]
3. Lionaki S, Derebail VK, Hogan SL, Barbour S, Lee T, Hladunewich M, Greenwald A, Hu Y, Jennette CE, Jennette JC, Falk RJ, Cattran DC, Nachman PH, Reich HN (2012) Venous thromboembolism in patients with membranous nephropathy. Clin J Am Soc Nephrol 7(1):43–51. 10.2215/CJN.04250511 [PubMed: 22076873]
4. Sexton DJ, de Freitas DG, Little MA, McHugh T, Magee C, Conlon PJ, O'Seaghdha CM (2018) Direct-acting oral anticoagulants as prophylaxis against thromboembolism in the nephrotic syndrome. Kidney Int Rep 3(4):784–793. 10.1016/j.ekir.2018.02.010 [PubMed: 29989039]
5. Zhang L, Zhang H, Zhang J, Tian H, Liang J, Liu Z (2018) Rivaroxaban for the treatment of venous thromboembolism in patients with nephrotic syndrome and low AT-III: a pilot study. Exp Ther Med 15(1):739–744. 10.3892/etm.2017.5471 [PubMed: 29399079]
6. 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 Pharmacomet Syst Pharmacol 6(5):340–349. 10.1002/psp4.12184
7. Cattran DC et al. (2012) Kidney disease: improving global outcomes (KDIGO) glomerulonephritis work group. KDIGO clinical practice guideline for glomerulonephritis. Kidney Int Suppl 2:186–197
8. Barbour SJ, Greenwald A, Djurdjev O, Levin A, Hladunewich MA, Nachman PH, Hogan SL, Cattran DC, Reich HN (2012) Disease-specific risk of venous thromboembolic events is increased in idiopathic glomerulonephritis. Kidney Int 81(2):190–195. 10.1038/ki.2011.312 [PubMed: 21918501]
9. Lee T, Biddle AK, Lionaki S, Derebail VK, Barbour SJ, Tannous S, Hladunewich MA, Hu Y, Poulton CJ, Mahoney SL, Charles Jennette J, Hogan SL, Falk RJ, Cattran DC, Reich HN, Nachman PH (2014) Personalized prophylactic anticoagulation decision analysis in patients with membranous nephropathy. Kidney Int 85(6):1412–1420. 10.1038/ki.2013.476 [PubMed: 24336031]
10. Almutairi AR, Zhou L, Gellad WF, Lee JK, Slack MK, Martin JR, Lo-Ciganic WH (2017) Effectiveness and safety of non-vitamin K antagonist oral anticoagulants for atrial fibrillation and venous thromboembolism: a systematic review and meta-analyses. Clin Ther 39(7):1456–1478 e1436. 10.1016/j.clinthera.2017.05.358 [PubMed: 28668628]

11. Di Lullo L, Tripepi G, Ronco C, De Pascalis A, Barbera V, Granata A, Russo D, Di Iorio BR, Paoletti E, Ravera M, Fusaro M, Bellasi A (2018) Safety and effectiveness of rivaroxaban and warfarin in moderate-to-advanced CKD: real world data. J Nephrol 10.1007/s40620-018-0501-7
12. Holster IL, Valkhoff VE, Kuipers EJ, Tjwa ET (2013) New oral anticoagulants increase risk for gastrointestinal bleeding: a systematic review and meta-analysis. Gastroenterology 145(1):105–112 e115. 10.1053/j.gastro.2013.02.041 [PubMed: 23470618]
13. Miller CS, Dorreen A, Martel M, Huynh T, Barkun AN (2017) Risk of gastrointestinal bleeding in patients taking non-vitamin K antagonist oral anticoagulants: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 15(11):1674–1683 e1673. 10.1016/j.cgh.2017.04.031 [PubMed: 28458008]
14. Gugler R, Shoeman DW, Huffman DH, Cohlmia JB, Azarnoff DL (1975) Pharmacokinetics of drugs in patients with the nephrotic syndrome. J Clin Investig 55(6):1182–1189. 10.1172/JCI108035 [PubMed: 1133166]
15. Eliquis (package insert) (2012) Bristol-Myers Squibb, Princeton, NJ
16. FDA product information warfarin. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/009218s107lbl.pdf. Accessed 1 May 2018
17. FDA product information apixaban. https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/021345s010lbl.pdf. Accessed 1 May 2018
18. FDA product information edoxoban. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206316lbl.pdf. Accessed 1 May 2018
19. FDA product information rivaroxaban. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202439s001lbl.pdf. Accessed 1 May 2018
20. FDA product information dabigatran. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202439s001lbl.pdf. Accessed 1 May 2018
21. FDA product information fondaparinux https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/021345s010lbl.pdf. Accessed 1 May 2018
22. Samama MM, Gerotziafas GT (2003) Evaluation of the pharmacological properties and clinical results of the synthetic pentasaccharide (fondaparinux). Thromb Res 109(1):1–11 [PubMed: 12679126]

Table 1

Characteristics of warfarin, DOACs, and fondaparinux

	Mechanism of action	% plasma protein bound	T_{max} [a] (h)	Half-life (h)	Route of elimination
Warfarin [16]	Vitamin K antagonist	99	2–6	40	Hepatically metabolized
Apixaban [17]	Direct inhibitor of factor Xa	87	3–4	8–15	27% renal
Edoxaban [18]	Direct inhibitor of factor Xa	55	1–2	10–14	50% renal
Rivaroxaban [19]	Direct inhibitor of factor Xa	92–95	2–4	5–9 (11–13 in elderly)	66% renal
Dabigatran [20]	Direct inhibitor of thrombin (factor IIa)	35	1.5–2	12–17	80% renal
Fondaparinux [21]	Antithrombin III-mediated selective inhibition of factor Xa	0[b]	3	17–21	77% renal

[a] Time to maximum concentration

[b] 94% bound to antithrombin III

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