Hospital Pharmacy
2022, Vol. 57(6) 774–778

DOI: 10.1177/00185787221108715
journals.sagepub.com/home/hpx
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Coronavirus Disease 2019-Related Extensive Thrombosis in a Patient Receiving Therapeutic Anticoagulation With Dabigatran

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Abstract

Introduction and Objective: Coronavirus disease 2019 (COVID-19) is associated with respiratory failure and a hypercoagulable state. Studies have shown the use of oral anticoagulants, specifically dabigatran, can significantly decrease mortality from COVID-19. Dabigatran is an oral direct thrombin inhibitor commonly used for nonvalvular atrial fibrillation and for the treatment or prevention of venous thromboembolism. The association of COVID-19-related extensive thrombosis while receiving full therapeutic anticoagulation with dabigatran has not been well-established in current literature. **Case Report:** We present a 73-year-old male patient with a history of persistent atrial fibrillation anticoagulated with dabigatran presenting with an active COVID-19 infection admitted to the intensive care unit. On hospital day 7, he developed extensive arterial and venous thromboembolisms. To our knowledge, this is the first published case of COVID-19-related extensive thrombosis while receiving full therapeutic anticoagulation with dabigatran. **Discussion:** Guidelines recommend prophylactic or therapeutic-dose anticoagulation with unfractionated heparin or low-molecular weight heparin for all patients if no contraindications exist; however, recommendations for the use of therapeutic oral anticoagulants have not been well established. Further studies are warranted to establish appropriate use of oral anticoagulants in the setting of COVID-19. **Conclusion:** Evidence from this report suggests clinicians should closely monitor patients at risk for hypercoagulability regardless of the anticoagulation therapy the patient may be receiving. Additionally, evidence from this case suggests a possible inferiority in the anticoagulation ability of dabigatran in patients with active COVID-19.

Keywords
critical care, anticoagulants, COVID, pharmacokinetics

Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is commonly associated with respiratory failure and a hypercoagulable state.[1,2] The increased systemic inflammatory response to COVID-19 is believed to be the driving force for hypercoagulability, specifically increases in the cytokine IL-6 leading to increased production of fibrinogen and platelets.[2,3] Changes in D-dimer, partial thromboplastin time, platelet count, and fibrinogen may present 4 to 10 days after hospitalization and indicate potential COVID-19-induced alterations to coagulation.[3] The use of direct oral anticoagulants (DOACs) prior to being admitted with COVID-19 has been associated with a significantly improved mortality, specifically with the use of dabigatran.[4]

Dabigatran is an oral anticoagulant that acts by inhibiting thrombin directly, which prevents the cleavage of fibrinogen to fibrin, thrombin-induced platelet aggregation, and inhibits the activation of factors V, VIII, XI, and XIII. It is commonly used to prevent stroke and embolism in patients with nonvalvular atrial fibrillation (NVAF) or for the treatment or prevention of venous thromboembolism (VTE).

There has been a case report of a patient developing pulmonary embolism on dabigatran after recovering from a COVID-19 infection.[1] Here, we present a case that, to our

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knowledge, is the first case report of COVID-19-related extensive thrombosis while receiving full therapeutic anticoagulation with dabigatran.

Case Report

The patient was a 73-year-old white male with a past medical history of Guillain-Barre syndrome (diagnosed 17 months prior to admission), hyperlipidemia, persistent NVAF (diagnosed 16 months prior to admission), and obesity (body mass index [BMI] on admission was 33.3 kg/m^2 [115 kg]). Additionally, he had an extensive surgical history (all of which occurred greater than 1 year prior to admission) including a left tibia fracture repair, right knee replacement, right rotator cuff repair, and left rotator cuff repair. He reported no significant family history, had a previous smoking history (quit 10 years prior to presentation), and reported no use of alcohol or illicit drugs. He reported good medication adherence to his home medications, which included dabigatran 150 mg by mouth twice daily, and metoprolol succinate 100 mg by mouth every morning and 50 mg by mouth every evening. He also reported taking a non-prescription fish oil supplement daily by mouth, dose unspecified. He reported no known medication allergies or adverse drug reactions.

The patient presented to the emergency department after approximately 2 weeks of rhinorrhea, congestion, and nonproductive cough. He complained of worsening fatigue and cough in the days leading to admission. He was found to be COVID-19 positive by polymerase chain reaction (PCR) testing. Of note, he had not received the COVID-19 vaccination due to his history of Guillain-Barre per advice from his primary care physician. In the emergency department, he was started on non-invasive positive pressure mechanical ventilation for hypoxia and an intravenous (IV) diltiazem infusion for his atrial fibrillation with rapid ventricular rate (RVR). He was admitted to the medical intensive care unit (MICU) for acute hypoxic respiratory failure secondary to COVID-19 pneumonia. He was continued on metoprolol for rate control and dabigatran to prevent stroke and systemic embolism. His IV diltiazem infusion was converted to diltiazem extended-release oral formulation and the dose was adjusted as indicated for rate control. He was initiated on remdesivir daily for 5 days (1 dose of 200 mg IV, followed by 4 doses of 100 mg IV) and dexamethasone daily for 10 days (1 dose of 6 mg IV, followed by 9 doses of 6 mg orally) for the management of COVID-19.

Pertinent laboratory tests can be seen in Table 1 for the first 8 days of the hospital stay. On hospital day 7, he reported acute pain and paresthesia of the right leg from mid-tibia and distally. Upon exam, his right foot was cold and pale compared to his left side. Additionally, a pedal pulse could not be palpated or located with bedside doppler ultrasound. Vascular surgery was consulted, and a stat computed tomography angiography (CTA) was ordered due to concern for acute limb ischemia. The CTA showed moderate volume pulmonary emboli, extensive arterial thrombus extending from the distal aorta through the majority of the right iliac arteries, and branch artery occlusions of large portions of the left kidney. Vascular surgery recommended transitioning anticoagulation to an IV unfractionated heparin (UFH) infusion given the development of thrombus while anticoagulated on therapeutic dabigatran. Due to a high risk of repeat thrombosis, surgical intervention was deferred. Since admission, he had not missed any doses of dabigatran.

The patient was transitioned to an IV UFH infusion (titrated to a goal anti-factor Xa level of 0.3-0.7 International units/mL) from hospital day 7 until hospital day 12, at which point he was converted to therapeutic enoxaparin (dosed as 1 mg/kg subcutaneously [SC] twice daily). On hospital day 16, he started warfarin and continued on therapeutic enoxaparin until his International Normalized Ratio (INR) was within his goal range of 2.0 to 3.0. Due to the need for invasive mechanical ventilation and requirement for amiodarone for refractory atrial fibrillation, warfarin was discontinued, and he was placed back on a therapeutic enoxaparin on hospital day 27. He was later transitioned back to an IV UFH infusion on day 30 after developing an acute kidney injury. On hospital day 32, after days of developing progressive multiorgan failure, life-sustaining treatment was withdrawn, and the patient died.

Discussion

Reports of VTE and arterial thromboembolism (ATE) have been common since the start of the COVID-19 pandemic, which have led to recommendations regarding the use of anticoagulants for prophylaxis in this hypercoagulable state.[2,3,5] In the beginning of the pandemic, recommendations using prophylactic-dose low-molecular-weight heparin (LMWH) or UFH were not sufficient and led to breakthrough thrombosis.[5] This prompted further studies to compare the use of therapeutic-dose versus intermediate dose versus prophylactic dose anticoagulation.[5,6] Current anticoagulation recommendations for patients with COVID-19 receiving intensive care unit level of care includes prophylactic-dose UFH or LMWH for all patients as long as no contraindications exist, according to the Society of Critical Care Medicine, Surviving Sepsis Campaign, and the National Institutes of Health (NIH).[6,7]

Additionally, the NIH recommends full-strength LMWH/UFH for non-critically ill patients over prophylactic-dose and is preferred over the use of DOACs.[6] This recommendation is based off multiple studies showing a significant benefit using therapeutic dosing in patients with COVID-19. In these studies, therapeutic dosing could have included any LMWH at the manufacturer's recommended therapeutic dosing or UFH titrated to therapeutic effect based on partial thromboplastin time (PTT) or anti-factor Xa monitoring per institutional protocol. The preferred agent was enoxaparin at

Table 1. Labs Collected During Hospital Days 1 to 8.

Lab test *[reference range]*	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
AST (U/L) *[0-45]*	35					44	32	33
ALT (U/L) *[0-40]*	30					58	47	46
CRP (mg/dL) *[<0.3-0.5]*		14						
ANC (k/cmm) *[1.8-7.8]*	7.43	4.86				15.91		
PTT (sec) *[23.0-37.7]*	16.4						>200	67.0
PT (sec) *[12.2-14.8]*	39.3							
INR *[0.9-1.2]*	1.3							
WBC (k/cmm) *[4.6-10.8]*	8.35	5.28	12.19	11.13	13.0	17.29	14.39	15.08
Hgb (g/dL) *[13.9-18]*	18.4	16.3	16.1	14.9	16.1	17.4	15.3	15.2
HCT (%) *[41-52]*	52.3	46.7	46.1	42.5	45.7	49.6	42.9	42.8
Plt (k/cmm) *[130-440]*	164	141	198	184	210	205	160	165
Glucose (mg/dL) *[65-99]*	119	148	142	146	132	117	119	172
BUN (mg/dL) *[9-20]*	27	24	24	24	24	22	23	24
Creatinine (mg/dL) *[0.5-1.2]*	1.1	0.8	0.7	0.7	0.9	1.0	0.8	0.9
Sodium (mmol/L) *[135-145]*	138	136	138	140	139	139	135	134
Chloride (mmol/L) *[23-32]*	102	104	105	107	105	102	101	99
CO2 (mmol/L) *[23-32]*	19	21	20	20	21	22	24	22
Potassium (mmol/L) *[3.5-5.0]*	4.0	4.7	3.9	3.9	4.0	4.0	4.3	4.4

Note. ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CO_2 = serum bicarbonate; CRP = C-reactive protein; HCT = hematocrit; Hgb = hemoglobin; INR = international normalized ratio; Plt = Platelets; PT = prothrombin time; PTT = partial thromboplastin time; WBC = white blood cells.

a dose of 1 mg/kg SC twice daily. Further, typical prophylactic dosing was enoxaparin 40 mg SC daily or heparin 5000 units SC 2 to 3 times daily based on institutional protocol. Regarding safety, a non-significant increase in non-fatal bleeding (defined based on International Society on Thrombosis and Haemostasis [ISTH] criteria as fatal bleeding, symptomatic bleeding in a critical area or organ, or bleeding causing a drop in hemoglobin of at least 20 g/L) was observed for the therapeutic dosing group.[8,9]

One concern with using DOACs compared to LMWH or UFH in general is the increased drug interactions present; however, most of these interactions lead to increased systemic concentrations. Decreased systemic concentrations of dabigatran can occur with the concomitant use of medications that increase the gastric pH or induce the P-glycoprotein efflux pump.[10] Medications that increase the gastric pH (eg, magnesium or aluminum-containing antacids) decrease the absorption of dabigatran, whereas medications that induce the P-glycoprotein efflux pump (eg, carbamazepine, phenytoin) may reduce the bioavailability of dabigatran by increasing drug efflux back into the intestinal lumen for excretion.[10] From hospital admission to the development of extensive thrombus, our patient did not receive any concomitant medications that could have explained any change in the systemic concentration of dabigatran. Of note, the patient did not receive any stress ulcer prophylaxis. Our patient did not have risk factors present to indicate an increased risk of clinically important gastrointestinal bleeding (eg, at least 48 hours of mechanical ventilation, platelets $<50\,k/mm^3$, INR >1.5, PTT >2 times baseline), so stress ulcer prophylaxis was not indicated.[11] Another major concern with dabigatran is the storage of the medication. Dabigatran must be stored in its original packaging to minimize product breakdown from moisture and avoid a loss of potency.[10] While our patient's home storage conditions of dabigatran are unknown, our facility uses manufacturer blister packs of dabigatran while inpatient to control for these storage conditions. The last major concern with the use of DOACs involves their efficacy in the obese patient population, especially with our patient having a BMI of $33.3\,kg/m^2$. Dabigatran has been reported to have significantly reduced plasma concentrations by about 20% in patients weighing more than 100 kg compared to patients weighing 50 to 100 kg[10,12] While there is limited data on therapeutic failure of dabigatran in patients with a BMI 30 to $40\,kg/m^2$, the available case reports of patients with a BMI greater than $40\,kg/m^2$ supports the idea of increased body weight significantly contributing to the diminished effect of dabigatran. The definitive reason for the lack of therapeutic efficacy of dabigatran in our patient case remains unclear, although the elevated BMI could have played a significant role.

While the findings in this case are noteworthy, this case report also has some important limitations. Most importantly, several coagulation/inflammatory tests (D-dimer, C-reactive protein (CRP), ferritin, and fibrinogen) were not collected at baseline and have limited data during his admission; however, these inflammatory markers can also be elevated in the absence of an active thrombosis and would not definitively indicate a thrombus. Additionally, the PTT, prothrombin time (PT), and INR were not continuously collected during

the first 7 days of admission to determine any changes in his coagulable state. These tests are not specific in assessing the anticoagulation effects of DOACs; however, elevations in these values may have shown some therapeutic effect of dabigatran. While not validated for determining therapeutic anticoagulation, an alternative approach that may warrant future studies is the use of thromboelastography (TEG) monitoring in patients with hypercoagulable states. Studies assessing the use of TEG monitoring in COVID-19 patients have reported it to be an effective strategy in guiding goal-directed anticoagulation of COVID-19 patients to improve patient outcomes.[13,14] Another important limitation to consider in this case report involves effects of COVID-19 that have not been studied that could have played a role in this thrombosis event. For example, it has been shown certain infections such as human immunodeficiency virus (HIV) have been shown to increase the expression of P-glycoprotein and increase the efflux of substrate medications.[15] While different in etiology and pathophysiology, both HIV and COVID-19 are associated with increased synthesis of pro-inflammatory cytokines leading to prolonged inflammation.[16] Similar to COVID-19, evidence suggests patients with chronic HIV infection are associated with a significantly increased risk of VTE; however, whether the increased systemic inflammatory response is the driving force of hypercoagulability has yet to be determined.[2,3,16,17] Due to the hypercoagulable state in HIV patients, it is recommended to use either LMWH or warfarin rather than DOACs for VTE treatment.[17] Although the increased expression of P-glycoprotein has not yet been confirmed in COVID-19, it would help account for a decreased serum concentration of dabigatran and explain the thrombosis event.

As described in the case, extensive ATE and VTE developed in the presence of a COVID-19 infection despite receiving therapeutic anticoagulation with dabigatran. While several studies have evaluated the use of anticoagulation in the setting of COVID-19, recommendations for the use of therapeutic DOACs in this setting have not been well established. One study of 497 patients compared the use of anticoagulation prior to admission with COVID-19 to assess for overall survival and thrombotic events. Although this study saw a low proportion of patients (less than 6%) in each group with thrombotic events, hazard ratios showed a significantly improved survival with the prior use of DOACs compared to no anticoagulation. In a secondary analysis, this study also found survival was significantly improved in patients over the age of 70 who were previously prescribed a DOAC. Additionally, all patients prescribed dabigatran in this study survived; thus, the authors of the study identified dabigatran as a potentially beneficial treatment needing further investigation.[4] Because this finding is in opposition of our patient case, further investigation is warranted as it remains unclear how to properly manage the anticoagulation regimen for patients on a DOAC with COVID-19 to prevent VTE or ATE events.

Conclusion

In conclusion, this case is the first to associate therapeutic failure of dabigatran leading to extensive thrombosis with an active COVID-19 infection. Evidence from this report suggests clinicians should closely monitor patients at risk for hypercoagulability regardless of the anticoagulation therapy the patient may be receiving. Additionally, evidence from this case suggests a possible inferiority of dabigatran-based therapeutic anticoagulation in patients with COVID-19. Further studies are warranted to establish appropriate anticoagulation in the setting of COVID-19.

Acknowledgments

This material is the result of work supported with resources and facilities of the U.S. Department of Veterans Affairs. The contents do not represent the views of the U.S. Department of Veterans Affairs or the United States Government. The authors have no conflicts of interest to disclose. Portions of this project have been reported previously in abstract form.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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References

1. D'Elia E, Gori M, Grosu A, et al. An unexpected case of recurrence of pulmonary embolism in a patient recovered from COVID19 in full regimen dose of direct oral anticoagulant drug. *BMC Pulm Med*. 2021;21:102. doi:10.1186/s12890-021-01453-2
2. Hadid T, Kafri Z, Al-Katib A. Coagulation and anticoagulation in COVID-19. *Blood Rev*. 2021;47:100761. doi:10.1016/j.blre.2020.100761
3. Gómez-Mesa JE, Galindo-Coral S, Montes MC, Muñoz Martin AJ. Thrombosis and coagulopathy in COVID-19. *Curr Probl Cardiol*. 2021;46:100742. doi:10.1016/j.cpcardiol.2020.100742
4. Buenen AG, Sinkeldam M, Maas ML, Verdonschot M, Wever PC. Prior use of anticoagulation is associated with a better survival in COVID-19. *J Thromb Thrombolysis*. 2021;52:1207-1211. doi:10.1007/s11239-021-02486-4
5. Giannis D, Douketis JD, Spyropoulos AC. Anticoagulant therapy for COVID-19: what we have learned and what are the unanswered questions? *Eur J Intern Med*. 2022;96:13-16. doi:10.1016/j.ejim.2021.11.003

6. COVID-19 Treatment Guidelines Panel. *Information on COVID-19 treatment, prevention and research*. National Institutes of Health. Updated: May 31, 2022. Accessed January 24, 2022. https://www.covid19treatmentguidelines.nih.gov/
7. Surviving Sepsis Campaign Panel. *COVID-19 guidelines*. Society of Critical Care Medicine. 2020. Accessed January 24, 2022. https://sccm.org/SurvivingSepsisCampaign/Guidelines/COVID-19
8. Spyropoulos AC, Goldin M, Giannis D, et al. Efficacy and safety of therapeutic-dose heparin vs standard prophylactic or intermediate-dose heparins for thromboprophylaxis in high-risk hospitalized patients with COVID-19: the HEP-COVID randomized clinical trial. *JAMA Intern Med*. 2021;181:1612-1620. doi:10.1001/jamainternmed.2021.6203
9. The ATTACC, ACTIV-4a, and REMAP-CAP Investigators. Therapeutic anticoagulation with heparin in noncritically ill patients with COVID-19. *N Engl J Med*. 2021;385:790-802. doi:10.1056/NEJMoa2105911
10. Pradaxa (dabigatran etexilate mesylate) [package insert]. Boehringer Ingelheim Pharmaceuticals, Inc.; 2011.
11. Barletta JF, Bruno JJ, Buckley MS, Cook DJ. Stress ulcer prophylaxis. *Crit Care Med*. 2016;44(7):1395-1405. doi:10.1097/CCM.0000000000001872
12. Sebaaly J, Kelley D. Direct oral anticoagulants in obesity: an updated literature review. *Ann Pharmacother*. 2020;54:1144-1158. doi:10.1177/1060028020923584
13. Thomas AV, Lin KP, Stillson JE, et al. A case series of thromboelastography-guided anticoagulation in COVID-19 patients with inherited and acquired hypercoagulable states. *Case Rep Med*. 2021;2021:5568982. doi:10.1155/2021/5568982
14. Hartmann J, Ergang A, Mason D, Dias JD. The role of TEG analysis in patients with COVID-19-associated coagulopathy: a systematic review. *Diagnostics*. 2021;11:172. doi:10.3390/diagnostics11020172
15. Lopez P, Velez R, Rivera V, Rodriguez N, Yamamura Y. Characteristics of p-glycoprotein (pgp) upregulated in chronic cocaine users and HIV infected persons. *Retrovirology*. 2005;2:142.
16. Illanes-álvarez F, Márquez-Ruiz D, Márquez-Coello M, Cuesta-Sancho S, Girón-González JA. Similarities and differences between HIV and SARS-CoV-2. *Int J Med Sci*. 2021;18(3):846-851. doi:10.7150/ijms.50133
17. Bibas M, Biava G, Antinori A. HIV-associated venous thromboembolism. *Mediterr J Hematol Infect Dis*. 2011;3(1):e2011030. doi:10.4084/MJHID.2011.030