Thrombolysis and use of argatroban for the treatment of massive pulmonary embolism following anticoagulation failure in a patient with COVID-19

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Purpose. Successful use of alteplase and argatroban to treat a patient with coronavirus disease 2019 (COVID-19)–associated massive pulmonary embolism with cardiac arrest is reported.

Summary. This case report describes a 42-year-old male with COVID-19 who developed a massive pulmonary embolism resulting in cardiac arrest after suspected failure of low-molecular-weight heparin therapy for a deep venous thrombosis. Administration of two 50-mg doses of intravenous alteplase resulted in return of spontaneous circulation, and low-dose argatroban was used as follow-up anticoagulation therapy without complications. This is the first case report of use of argatroban in a patient with COVID-19 with cardiac arrest–associated massive pulmonary embolism after failure of previous anticoagulation efforts.

Conclusion. Argatroban may be used as an alternate anticoagulation strategy in COVID-19 patients who fail low-molecular weight therapy. A risk versus benefit discussion should be had regarding appropriateness of therapy as well as dosing. More data is needed to understand the unique hypercoagulable condition in COVID-19 patients as well as research that further highlights the role of argatroban and bivalirudin therapy in this patient population.

Keywords: anticoagulants, argatroban, COVID-19, heart arrest, pulmonary embolism, tissue-plasminogen activator

Am J Health-Syst Pharm. 2020; XX:XX-XX

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Venous thromboembolism (VTE) is a broad term used to describe a deep venous thromboembolism (DVT) or a pulmonary embolism (PE). Compared to ambulatory care patients, patients admitted to an intensive care unit (ICU) may have additional risk factors for VTE, including mechanical ventilation, insertion of central venous catheters, and sepsis.[1] Additionally, emerging data suggest that patients with a diagnosis of coronavirus disease 2019 (COVID-19) may develop a hypercoagulable state related to severe inflammation and hemostatic pathway imbalances that increase the risk of complications related to clot formation.[2-8]

Treatment of a VTE typically involves the use of unfractionated heparin or low-molecular-weight heparin (LMWH); however, in a rare subset of patients anticoagulation therapy may fail, and those patients require treatment escalation. Cardiac arrest as a result of a massive PE is associated with a high mortality rate and requires prompt treatment with intravenous thrombolysis.[9] If the patient survives, a risk-benefit analysis that involves the careful consideration of intravenous anticoagulation and close monitoring of therapy efficacy should occur.

Here we describe a case in which a patient with COVID-19 developed a massive PE leading to cardiac arrest despite receiving therapeutic anticoagulation for a DVT. The patient was treated successfully with alteplase and argatroban therapy.

Case report

A 42-year-old male with a past medical history of asthma presented to our institution's emergency department with hypoxemia, shortness of breath, chest tightness, and a chest x-ray showing bilateral patchy heterogeneous opacities after diagnosis of COVID-19 eight days previously. Supportive care was initiated with scheduled albuterol along with as-needed guaifenesin and use of a nonrebreather mask for airway support. Despite initial management, the patient experienced worsening oxygenation requiring intubation. With a ratio of arterial partial pressure of oxygen (Pao_2) to fraction of inspired oxygen (Fio_2) of 98, the patient was diagnosed as having severe acute respiratory distress syndrome (ARDS). He was therapeutically paralyzed for 4 days with a vecuronium continuous infusion and maintained in a prone position for 2 days. Since the patient's D-dimer concentration was greater than 3,000 ng/mL on admission, he received DVT prophylaxis with enoxaparin (0.5 mg/kg subcutaneously every 12 hours), as was appropriate per our institution's policy for anticoagulation in patients with COVID-19.[10,11]

KEY POINTS

- Thromboembolism is a growing concern in treatment of patients with COVID-19.

- Direct thrombin inhibitors can be used as an alternative anticoagulation strategy if there is concern for failure of low-molecular-weight heparin therapy.

- A greater understanding of the pathophysiology of thromboembolism in COVID-19 is needed to better guide prevention measures.

After 4 days of therapeutic paralysis, a lower extremity DVT was detected via Doppler scan, and the patient was switched to enoxaparin 1 mg/kg every 12 hours, with dose calculated using actual body weight. Over the next 4 days, the patient improved with supportive care consisting of nebulized bronchodilators, mucolytics, diuretics, and epoprostenol therapy; he was weaned off paralytics and completed COVID-19 treatment courses of hydroxychloroquine and tocilizumab. Mechanical ventilation requirements improved, with an increase in the Pao_2/Fio_2 ratio to 240, and the patient had minimal vasopressor requirements. On the morning prior to cardiac arrest, the only component of the disseminated intravascular coagulation (DIC) panel that was abnormal was a prothrombin time of 13 seconds. Coagulation-related laboratory values, including D-dimer level, improved beginning on admission day 8, as detailed in Table 1. With the overall improvement there were discussions of attempting spontaneous breathing trials, given that the patient was much more stable.

On the evening of admission day 8, the patient went into cardiac arrest. Over the course of 20 minutes the patient lost and regained a pulse, switching back and forth from pulse electrical activity (PEA) arrest to ventricular tachycardia. It was determined that the patient had a massive PE, and the decision was made to administer thrombolytic therapy. Two 50-mg doses of alteplase were mixed at the bedside by pharmacy staff in accordance with guideline recommendations and case reports of success improving survival

Table 1. Patient's Coagulation-Related Laboratory Values

ICU Day	D-dimer, ng/mL[a]	aPTT, s	Fibrinogen, mg/dL	Antithrombin, %	Anti-Xa, unit/mL	Critical Events	Anticoagulation Treatment
3	1,124	. . .[b]	. . .[b]	104	. . .[b]	Paralysis on day 1, prone on day 1	Enoxaparin 0.5 mg/kg subcutaneously q 12 h
4	928-1,123	39	>1,000	98	. . .[b]	Paralysis on day 2, prone on day 2	
5	1,252	37.7	>1,000	110	. . .[b]	Paralysis on day 3	
6	5,486	34.2	906	108	. . .[b]	Paralysis on day 4; DVT diagnosed	Enoxaparin 1 mg/kg subcutaneously q 12 h
7	17,868	33.2	625	117	. . .[b]	No significant events	
8	5,692	35	433	111	0.88[c]	No significant events	
9[d]	4,686-6,081	37.2-85.1	262-336	103	. . .[b]	PEA arrest	Argatroban initiated

Abbreviations: anti-Xa, anti–factor Xa antibody; aPTT, activated partial thromboplastin time; DVT, deep venous thrombosis; pulseless electrical activity.
[a]Initial D-dimer level was obtained on admission day 3.
[b]Not measured.
[c]Sampling performed at steady state approximately 4 hours post morning dose.
[d]Laboratory values measured on the morning prior to cardiac arrest secondary to massive pulmonary embolism.

with the use of bolus-dose alteplase therapy during cardiopulmonary resuscitation.[12-14] Each dose was given over 2 minutes and circulated by cardiopulmonary resuscitation for 15 minutes, with return of spontaneous circulation (ROSC) achieved after the second dose was administered. Afterward, pharmacy personnel were consulted for a recommendation regarding anticoagulation therapy after suspected failure of anticoagulation with LMWH. Argatroban was recommended in preference to unfractionated heparin and bivalirudin.

Discussion

A drug information search on PubMed using the Medical Subject Headings terms "Covid-19" and "thrombophilia" or "pulmonary embolism" produced over 45 articles that address the coagulation abnormalities associated with COVID-19. During the initial write-up of this case report, there were only a handful of published reports available to guide clinicians in understanding COVID-19–associated anticoagulation abnormalities as they relate to thromboembolism.[2-4]. At the time of the patient's cardiac arrest, only 1 of these articles had been published and was available online. Tang et al[4] studied the coagulation patterns of 183 patients in Wuhan, China, and found that those who did not survive were more likely to have elevations in D-dimer, lower fibrinogen levels, and prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT), which are suggestive of DIC. Since the time of this case report, there is a better understanding of the incidence of COVID-19–related thrombotic complications, which may occur in up to one-third of patients; their complex pathophysiology, which involves compliment-driven destruction of the capillaries and proinflammatory cytokine storms; and the need for earlier monitoring of coagulation.[7,8,15,16] Around the time of the case reported here, our institution had just started implementing a protocolized approach to addressing these thrombotic

concerns through more frequent coagulation monitoring, including daily DIC panels.[11]

Table 1 shows coagulation test results for the patient described in this case report. It should be noted that the patient was prescribed DVT prophylaxis on the first day of ICU admission; however, the patient refused enoxaparin doses the first 2 days of therapy (ICU admission days 1 and 2). On ICU admission day 8 an anti–factor Xa level determination ordered for monitoring of enoxaparin therapy was found to be within the goal range at steady state. Fibrinogen levels were initially elevated, suggesting a procoagulant state, but decreased during monitoring, which was consistent with the previously described pathophysiology of coagulation abnormalities.[4] The elevation in D-dimer level was the most prominent and consistent laboratory value suggesting a thromboembolic state, and the level remained elevated on ICU admission day 9, when the patient went into cardiac arrest secondary to suspected PE. The D-dimer level is a nonspecific laboratory value that can be used adjunctively with appropriate imaging to diagnose VTE, but in a critically ill patient it can be elevated due to many other factors, including infection, renal dysfunction, and disseminated intravascular disorder.[1] While the patient had several risk factors for the development of VTE, including mechanical ventilation, obesity, and immobility due to 4 days of paralysis with vecuronium, the patient received appropriate anticoagulation and monitoring. Treatment failure was determined by the team to most likely be a result of a hypercoagulable state associated with COVID-19.

During ROSC, the primary team discussed the use of anticoagulation following initial treatment failure with LMWH therapy. While theoretically unfractionated heparin could have been used, given the patient's stable antithrombin levels throughout admission, there was great concern in using a heparin analog because the patient had developed a life-threatening clot

despite appropriate anti-Xa monitoring. Given the tenuous nature of the patient after cardiac arrest (he required maximal vasopressor support with 4 agents as well as antiarrhythmic treatment for unstable ventricular tachycardia), an anticoagulant from a different pharmacologic class was preferred. Thus, a direct thrombin inhibitor, with aPTT monitoring, was recommended.

Argatroban and bivalirudin are both direct thrombin inhibitors that can be used as anticoagulation alternatives for the treatment of heparin-induced thrombocytopenia (HIT). Argatroban has been used for the of treatment PE in patients with HIT and has a Food and Drug Administration–approved indication for that purpose.[17] Bivalirudin can be used off-label for HIT and has been studied more extensively in cardiac patients undergoing percutaneous coronary intervention for acute coronary syndromes.[18,19] The success of bivalirudin use after thrombolysis for massive PE has been previously described.[20]

There is a limited body of data on the use of argatroban outside of its use in anticoagulation for HIT, and to our knowledge there are no published studies evaluating the use of argatroban or bivalrudin for the treatment of PE after LMWH treatment failure in patients with COVID-19. Familiarity with monitoring and dosing, the weight of evidence from studies in the medical intensive care patient population, and cost were factors favoring the recommendation of argatroban.[21-23] Anticoagulation was initiated soon after ROSC was achieved, and concerns for hemoptysis were addressed through use of a reduced dosage (0.5 µg/kg per minute), with aPTT monitoring occurring every 2 hours until attainment of an aPTT goal (60–89 seconds) according to the institution's nurse-driven anticoagulation protocol. A low-dose protocol was recommended, despite initial concern for a risk of undertreating the patient's hypercoagulable state, after consideration of the risks of major bleeding after

thrombolysis and his borderline Child-Pugh score of 6. Additionally, the patient experienced hemoptysis requiring treatment with 1 dose of inhaled tranexamic acid shortly after thrombolysis, further solidifying the decision to start low-dose argatroban in conjunction with close monitoring of bleeding. The patient's aPTT values reached the therapeutic range after 48 hours at an argatroban dosage of 2.86 µg/kg per minute, and therapy was continued for 7 days until the patient was switched to apixaban and discharged 2 days later. Of note, the patient did not suffer any neurologic deficits related to prolonged cardiac arrest.

Conclusion

This case report describes the successful use of argatroban after thrombolysis in a patient with cardiac arrest related to a massive PE. Despite a lack of data to guide anticoagulation monitoring in patients with COVID-19, using a reduced initiation dose of argatroban and titrating the dose to achieve standardized aPTT values proved to be a reasonable approach to care.

More data are needed to better understand the hypercoagulable condition of patients with COVID-19, and randomized controlled trials of anticoagulation strategies in the context of COVID-19 are needed to identify the best approach to preventing and treating VTE in these patients.

Disclosures

The authors have declared no potential conflicts of interest.

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