SOLVING CLINICAL PROBLEMS IN BLOOD DISEASES

A physician or a group of physicians considers presentation and evolution of a real clinical case, reacting to clinical information and data (boldface type). This is followed by a discussion/commentary.

Argatroban and catheter-directed thrombolysis with alteplase for limb- and graft-threatening thromboses in a patient with a history of HIT

Angela Maldonado*[1,2]

A 73-year-old, 6′0″, 130 kg, white male who is self-employed as a farmer presented to the hospital with a chief complaint of severe nausea, vomiting, and diarrhea accompanied by dizziness and diaphoresis occurring since that morning. His family and social history were noncontributory. On examination, the patient appeared comfortable and in no acute distress. The blood pressure was 92/56 mmHg, the pulse 68 beats per minute, the temperature 97.6°F, the respiratory rate 18 breaths per minute, and the oxygen saturation 95% on room air. Lung sounds were diminished bilaterally in the bases. The remainder of a 10-point review of systems was negative except for an elevated serum creatinine (1.6, 1.2 mg/dL baseline), BUN (30 mg/dL), and white blood cell count (14.4 K/μL).

The patient's initial presentation was consistent with a bacterial or viral gastroenteritis along with acute renal failure secondary to volume depletion. Other factors that predisposed him to gastrointestinal symptoms included long-term immunosuppression with mycophenolate mofetil as well as uremia.

The patient has an extensive medical history that includes relevant disease states. The patient is 5 years post living donor kidney transplant secondary to chronic renal failure from ischemic nephropathy. His course immediately following transplant was complicated by deep venous thromboses in the right femoral and popliteal veins and pulmonary embolism secondary to hypercoagulability disorders including documented elevated anticardiolipin IgM antibody and protein S deficiency in the setting of a normal protein C level. Heparin and warfarin therapy had been initiated at the time of diagnosis. He developed thrombocytopenia and a heparin-induced thrombocytopenia (HIT) antibody test was reported in the record as weakly positive. He was subsequently treated with fondaparinux and warfarin but developed a diverticular bleed within ~1 month. Anticoagulation was discontinued and an inferior vena cava filter was placed. The patient then opted against chronic anticoagulation. His current medications at the time of admission include alendronate, allopurinol, aspirin, calcium carbonate, carvedilol, ferrous sulfate, fish oil, furosemide, glipizide, multivitamins, mycophenolate mofetil, pantoprazole, prednisone, tacrolimus, and tamsulosin. His listed allergies include an unknown reaction to atenolol, itching with cephalexin, and heparin-induced thrombocytopenia.

Upon admission, blood, stool, and urine cultures were obtained and subsequently were negative. FK506 and MMF levels were within normal limits making it unlikely that drug toxicity was causing his symptoms. An unenhanced abdominal CT demonstrated acute diverticulitis and the patient was started on ciprofloxacin and metronidazole for treatment.

On the 2nd day of admission, the patient's serum creatinine continued to rise and he became oliguric. He also developed bilateral lower extremity edema, pain, cyanosis, and mottling. Due to his worsening renal function, the patient developed metabolic acidosis and because of this, hemodialysis was initiated.

The patient was not started on deep vein thrombosis (DVT) prophylaxis upon admission because he had been ambulatory and had an IVC filter in place. Thrombosis was, however, suspected due to his extensive hypercoagulability history. The decision was made to transfer the patient to the intensive care unit.

Interventional radiology was consulted. Doppler ultrasound of his legs and kidney revealed extensive bilateral lower extremity deep vein thromboses and allograft transplant vein obstruction. At that time the reading physician recommended mechanical and/or chemical thrombolysis. The healthcare team decided to begin catheter-directed thrombolysis (CDT) with alteplase and systemic anticoagulation with the direct thrombin inhibitor argatroban due to the contraindication of using heparin in a patient with a history of HIT. Informed patient consent was obtained.

[1] Kidney Transplant Program, Providence Sacred Heart Medical Center, Spokane, WA; [2] Department of Pharmacotherapy, Washington State University, Spokane, WA

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*Correspondence to: Dr. Angela Maldonado, 101 W. Eighth Avenue, Spokane, WA 99204. E-mail: angela.maldonado@providence.org

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Catheter-directed thrombolysis is a viable option for treatment in patients that meet certain criteria [1]. Alteplase is often used in CDT due to its short half-life and lack of allergenicity. Alteplase is a recombinant tissue plasminogen activator (t-PA) that catalyzes the conversion of plasminogen to plasmin, thereby initiating thrombolysis. Alteplase is FDA-approved for the treatment of acute stroke, myocardial infarction, and pulmonary embolism [2]. Although its use in CDT for DVT is off-label, it is well documented in the literature and is endorsed by The Society of Interventional Radiology and the American College of Chest Physicians [1,3]. Standard of care for treatment of acute arterial occlusive disease may vary among institutions but two common regimens include 0.02–0.1 mg/kg/hr or 100 mg of alteplase to be given via catheter over at least 2 hr. Systemic anticoagulation with heparin is started or restarted at the end of the alteplase infusion. After successful treatment of the thrombus, it is recommended to commence anticoagulant therapy as per standard guidelines.

Baseline laboratory values were hemoglobin 13.9 g/dL, hematocrit 41.8%, platelets 127 K/μL, white blood cell 16.0 K/μL, INR 1.0, alanine aminotransferase 19 U/L, alkaline phosphatase 4.6 U/L, aspartate aminotransferase 21 U/L, total bilirubin 1.2 mg/dL and direct bilirubin 0.5 mg/dL. A heparin/PF4 antibody ELISA test was ordered (Diagnostica Stago, Parsippany, NJ).

Although most of the liver function tests were within normal limits, the patient had an unexplained elevation in both direct and total bilirubin. This was taken into consideration when calculating the dose of argatroban (see commentary). The platelet count was slowly declining and drug-induced causes were ruled out. In response to the declining platelet count in a HIT-positive patient, a HIT antibody test was ordered.

Argatroban was initiated just prior to the CDT at a dose of 5 mg/hr (0.75 mcg/kg/min using an actual body weight of 116 kg) in accordance with hospital protocol with a target aPTT of 50–75 (see commentary). The patient was intubated to protect the airway. Venous angiography was done to explore the extent of the DVT and to initiate CDT as indicated. Angiography revealed thrombotic regions in the inferior vena cava superior to the IVC filter, and inferiorly involving the iliac, common femoral, superficial femoral, and popliteal veins bilaterally. The right superficial femoral thrombosis appeared to be a chronic lesion. Venous flow could not be demonstrated in the allograft renal vein and blunting of Doppler wave forms suggested outflow obstruction. CDT using alteplase was initiated at 0.5 mg/hr. This procedure was repeated once more in 24 hr.

Once thrombolysis was achieved through CDT with alteplase, the use of heparin was contraindicated due to the patient's history of heparin-induced thrombocytopenia. The decision was made to use a direct thrombin inhibitor in place of heparin. Lepirudin and argatroban were evaluated. Argatroban was felt to be the most suitable agent since, unlike lepirudin, renal function has minimal effects on its pharmacokinetic or pharmacodynamic properties.

Argatroban was continued at 5 mg/hr. The patient's baseline aPTT was 30 sec and subsequent dosing changes were needed to achieve goal aPTT of 50–75 sec.

Argatroban is FDA-approved for the treatment or prophylaxis of thrombosis in patients with HIT or patients undergoing percutaneous coronary intervention (PCI) who have or are at risk for HIT [4]. The recommended dose per the manufacturer for HIT is 2 mcg/kg/min with a dose adjustment in hepatic impairment to 0.5 mcg/kg/min. The target aPTT is 1.5–3 times baseline. The institution's goal aPTT of 50–75 fits the range of 1.5–3 times an average patient's baseline. Argatroban's anticoagulant activity is affected by binding to the thrombin active site and inhibiting fibrin formation, activation of factors V, VIII, and XIII, activating protein C, and inhibiting platelet aggregation. The use of argatroban as an adjunct anticoagulant in this patient was off-label as the thrombi were not a direct result of HIT. The second HIT antibody optical density was 0.098 with a cut-off of $>$0.520 considered as positive. This was expected since the patient had not been exposed to heparin or heparin products in the 5 years since his first diagnosis of HIT.

Repeat Doppler ultrasound and angiography demonstrated patency of the left iliac vein with near complete resolution of the iliac and internal vena caval thrombosis as well as reperfusion of the allograft kidney. The patient had $>$200 mL of urine output in the first 24-hr post-procedure. Oral warfarin sodium was started on Day 4 of admission with a targeted INR range of 4–6 due to concomitant argatroban. The patient received a total of 2 days of CDT alteplase and 11 days of argatroban therapy. The patient was discharged after a total of 16 days with a patent allograft vein, a return to baseline renal status and functioning bilateral extremities on long-term warfarin anticoagulation.

Commentary

The simultaneous use of alteplase and argatroban is documented minimally in the literature [5–11]. To our knowledge, there is only one case report describing the use of concomitant alteplase and argatroban for the treatment of acute thrombosis in lower extremities. Turba et al. described an experience with CDT with alteplase and argatroban in a patient with acute arterial thrombosis as a direct result of developing HIT after exposure to subcutaneous heparin for DVT prophylaxis [5]. The patient received 1 mg/hr of intra-arterial alteplase and intra-arterial argatroban 350 mcg/kg bolus then 25 mcg/kg/min infusion with complete resolution of the occluded segments and no reported complications. The patient's baseline aPTT, INR goals, weight, and duration of overlap between argatroban and warfarin and argatroban dose adjustments were not disclosed to provide a direct comparison with our case. In contrast, we did not initiate bolus dosing with argatroban and the maintenance infusion dose was much more conservative. In addition, infusion of argatroban was initiated through a peripheral line rather than intra-arterially and duration of therapy lasted until a therapeutic INR was reached with warfarin.

Our patient presented a significant challenge to the medical team. Items that were factored into the decision process include: extensive clot burden in bilateral lower extremities, a clogged IVC filter, venous allograft vein thrombus with resultant acute renal failure, a history of HIT, a significant hypercoagulability profile and an elevated bilirubin. Multiple dosing changes were required to attain a therapeutic aPTT. In accordance with institutional protocol (Table I), argatroban was initiated at 0.75 mcg/kg/min, which is 37.5% of the recommended dose per package insert. It must be noted that the dosing in Table I is not FDA approved and was developed by amassing information from the literature as

TABLE I. Argatroban Dosing Guideline (Not FDA Approved)

Initial dose (mcg/kg/min)	aPTT less than 50	aPTT 50–75	aPTT 76–99	aPTT > 99
Patients with normal hepatic function and normal renal function				
1	Increase rate by 10–20%	No change	Decrease rate by 10–20%	Hold infusion for 1 hr, then restart at 50% of previous infusion rate
Patients with normal hepatic function and impaired renal function				
0.75	Increase rate by 10–20%	No change	Decrease rate by 10–20%	Hold infusion for 1 hr, then restart at 50% of previous infusion rate
Patients with hepatic dysfunction and normal renal function				
0.5	Increase rate by 10–20%	No change	Decrease rate by 10–20%	Hold infusion for 2 hr, then restart at 50% of previous infusion rate
Patients with hepatic dysfunction and impaired renal function				
0.25	Increase rate by 10–20%	No change	Decrease rate by 10–20%	Hold infusion for 2 hr, then restart at 50% of previous infusion rate

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well as incorporating in-hospital data and pharmacists' experiences with dosing argatroban. The doses are adjusted for hepatic and/or renal dysfunction based partly on recommendations from the manufacturer as well as data from published sources [12]. After the initiation of the argatroban infusion, the patient's aPTT was above the target goal. This may be explained by the elevated total bilirubin which peaked to 2.2 mg/dL on the second day of argatroban treatment and subsequently returned to normal limits by Day 5 of admission. This is a feasible assumption since argatroban is hepatically metabolized and cleared through biliary excretion. Frequency of monitoring was debated since there seemed to be a trend that a change in aPTT would not become apparent after a dosing change within 4 hr, which is the recommended interval for remonitoring aPTT. Extending the monitoring frequency may result in fewer empiric changes but may increase the risk of bleeding due to a supratherapeutic aPTT.

Given the successful experience with argatroban, coupled with concern regarding the patient's thrombocytopenia, argatroban was continued without switching to heparin. Mechanical or open thrombectomy were not considered an option due to the patient's low platelet count and extensive clot burden. Monotherapy with either a direct thrombin inhibitor or catheter directed thrombolysis alone were considered unsuitable due to his high risk of reocclusion in light of his hypercoagulability profile.

Warfarin was initiated at an average dose of 6.25 mg/day and the INR was advanced slowly due to an increased risk of coumadin-induced skin necrosis in the setting of protein S deficiency and took 14 days to reach target INR.

This patient's first apparent episode of HIT, occurring post-transplant ~5 years prior to this admission, was accompanied by a weakly-positive HIT antibody test (presumably an ELISA assay, but not confirmable from the record). Because he was not rechallenged with heparin, the HIT antibody test on this admission would be expected to be negative, and, in retrospect cannot be seen as either confirming or ruling out his prior episode of HIT.

This case represents successful treatment of limb and graft threatening lower extremity ischemia and acute kidney allograft vein occlusion with a combination of catheter-directed thrombolysis with tissue plasminogen activator and a direct thrombin inhibitor.

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References

1. Hirsh J, Guyatt G, Albers GW, et al. Antithrombotic and thrombolytic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133(6 Suppl):110S–112S; Erratum in: Chest 2008;134:473.
2. Cathflo™ Activase® [Alteplase] [package insert]. South San Francisco, CA: Genentech, Inc.; 2001.
3. Working Party on Thrombolysis in the Management of Limb Ischemia. Thrombolysis in the management of lower limb peripheral arterial occlusion—A consensus document. J Vasc Interv Radiol 2003;14:S337–S349.
4. Argatroban [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2008.
5. Turba UC, Bozlar U, Simsek S. Catheter-directed thrombolysis of acute lower extremity arterial thrombosis in a patient with heparin-induced thrombocytopenia. Catheter Cardiovasc Interv 2007;70:1046–1050.
6. Yamada K, Tsuji H, Kimura S, et al. Effects of argatroban and heparin on thrombus formation and tissue plasminogen activator-induced thrombolysis in a microvascular thrombosis model. Thromb Res 2003;109:55–64.
7. Boeve TJ, Reed GL, de Oliveira NC, et al. Comparison of argatroban and hirudin for the reperfusion of thrombotic arterial occlusion by tissue plasminogen activator. J Thromb Thrombolysis 1998;6:103–108.
8. Serebruany VL, Jang IK, Giugliano RP, et al. A randomized, blinded study of two doses of Novastan(R) (brand of argatroban) versus heparin as adjunctive therapy to recombinant tissue plasminogen activator (accelerated administration) in acute myocardial infarction: Rationale and design of the myocardial infarction using Novastan(R) and T-PA (MINT) study. J Thromb Thrombolysis 1998;5:49–52.
9. Valji K, Arun K, Bookstein JJ. Use of a direct thrombin inhibitor (argatroban) during pulse-spray thrombolysis in experimental thrombosis. J Vasc Interv Radiol 1995;6:91–95.
10. LaMonte MP, Stallmeyer MJ. Acute ischemic stroke successfully treated using sequenced intravenous and intra-arterial thrombolysis and argatroban anticoagulation: A case study. J Thromb Thrombolysis 2004;17:151–156.
11. Wong CK, White HD. Direct antithrombins: Mechanisms, trials, and role in contemporary interventional medicine. Am J Cardiovasc Drugs 2007;7:249–257.
12. Arpino PA, Hallisey RK. Effect of renal function on the pharmacodynamics of argatroban. Ann Pharmacother 2004;38:25–29.