A Review of an Unorthodox Argatroban Infusion Rate for Anticoagulation in a Patient Case

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Abstract: Argatroban is an intravenous DTI (direct synthetic thrombin inhibitor) that is not routinely used for anticoagulation; thus, expertise surrounding its use is very limited. Therefore, this case reviews an unusually high argatroban infusion rate, which was needed to prevent further emboli formation in a patient. In this case, a 61-year-old Caucasian male patient exhibited heparin resistance during an intraoperative vascular procedure as measured by activated clotting time and PTT (partial thromboplastin time). The patient had multiple occlusions in his right lower extremities and underwent embolectomies of the right popliteal and posterior tibial arteries. The clinical pharmacist was consulted to manage the argatroban infusion once heparin was discontinued. The therapeutic window required a PTT of 1.5–3 times the patient baseline (35–75 s). The patient was reported to be 89 kg with a baseline PTT of 24.7 s and INR (international normalized ratio) of 0.98. The starting dose of argatroban was initiated by the pharmacist at 2 mcg/kg/min (10.7 mL/h) as the patient did not have hepatic failure or sepsis. The patient was maintained on argatroban in the therapeutic PTT window for more than 72 h; however, frequent and aggressive dose increases, to a final rate of 7.5 mcg/kg/min (40 mL/h), were needed to maintain the therapeutic PTT level. From the case, the cause of heparin resistance still has not been determined despite a hematologic work-up; however, this patient required an unusually high infusion rate of argatroban to maintain a therapeutic PTT during the hospital course before being changed to an anticoagulation regimen for discharge.

Key words: Anticoagulation, argatroban, direct thrombin inhibitor, heparin resistance, partial thromboplastin time.

1. Introduction

Anticoagulants are used to provide blood-thinning properties to prevent thrombus formation. There are many commercially available anticoagulants with different mechanisms of action which include Vitamin K antagonists, direct thrombin inhibitors, factor Xa inhibitors, low-molecular weight heparins and heparin. There have been documented cases of heparin resistance, especially during cardiopulmonary bypass surgeries. Finley and Greenberg [1] defined heparin resistance in a surgical patient as the “inability of an adequate heparin dose to increase the ACT (activated clotting time) to the desired level” [1]. However, despite the unresponsiveness of the ACT, it is not well known if a patient will also have insufficient anticoagulation effects. ACT is mainly reserved for monitoring of a heparin infusion during

cardiopulmonary bypass surgery, as it is typically not the routine measure of heparin when other variables are present [2]. Many causes for heparin resistance have been discussed in the literature which include, but are not limited to, AT (antithrombin) mediated causes, such as reduced production or hastened heparin clearance, and non-AT mediated reasons, such as increased heparin-binding, platelet dysfunction, or other miscellaneous causes [1]. Additionally, in many patients, the presence of an elevated PTT (partial thromboplastin time) at baseline may depict the presence of a coagulopathy which may alter PTT results seen in heparin resistance [3].

Argatroban is an IV (intravenous), synthetic, direct thrombin inhibitor that is not routinely used for anticoagulation in clinical practice due to high medication cost, its short half-life requiring continuous infusion, and the need for frequent monitoring. It has FDA-approved indications for HIT (heparin-induced thrombocytopenia) and PCI (percutaneous coronary

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intervention) [4]. PTT is measured to ensure appropriate anticoagulation with argatroban when in the therapeutic range.

Because argatroban is not often utilized, and is identified by the ISMP (Institute of Safe Medication Practices) as a high-alert medication, there is unfamiliarity among healthcare professionals with appropriate dosing, monitoring, and bridging to oral anticoagulation; therefore, medical center policies are frequently implemented to prevent medication errors and improve patient safety [5]. At the DVAMC (Dayton Veterans Affairs Medical Center), a clinical pharmacist-run argatroban policy exists which has both decreased costs and increased patient safety at the medical center since implementation in January 2014. From quality data gathered after the medical center policy was initiated, patients requiring an argatroban infusion at the DVAMC have been maintained on a rate in the range of 0.2~2 mcg/kg/min.

2. Clinical Case

A 61-year-old Caucasian male presented to the emergency room with complaints of a cold and numb right leg. He has a past medical history significant for CAD (coronary artery disease) status post 2-vessel CABG (coronary artery bypass graft) in 2006, hyperlipidemia, bile duct obstruction with history of cholangitis and liver abscess, chronic obstructive pulmonary disease with continued tobacco use, and peripheral arterial disease. He has a past surgical history of cholecystectomy, CABG, ventral hernia

repair, angioplasty with stent in the right common femoral and iliac arteries, and left femoral popliteal bypass with a PTFE (polytetrafluoroethylene) graft.

On presentation, his right leg was found to be cold with blue/purple toes. He was taken to the OR (operating room) immediately for attempted reperfusion of his right lower extremity. In the OR, his ACT was found to be unresponsive to a therapeutic heparin infusion with continued clot propagation on the table, despite a measured PTT of 117.8 s. The internal medicine clinical pharmacy specialist was contacted to facilitate the switch to argatroban to provide more appropriate anticoagulation. The patient was reported to be 89 kg with a baseline PTT of 24.7 s and an INR (international normalized ratio) of 0.98. The therapeutic window for argatroban requires a PTT of 1.5~3 times the patient baseline (35~75 s). The starting dose of argatroban was initiated at 2 mcg/kg/min (10.7 mL/h) as the patient did not have hepatic failure or sepsis. The last LFTs (liver function tests) obtained before starting the argatroban drip were about two months prior with no abnormalities noted (Table 1).

PTTs were monitored every 2~4 h until two consecutive stable values within 35~75 s were obtained, after the patient arrived in the Intensive Care Unit following surgery. Over the next 72 h of the argatroban infusion, the patient was requiring consistent and aggressive increases in the argatroban infusion rate to maintain a therapeutic PTT (Table 2). The patient finally achieved a consistent therapeutic PTT value only after 72 h of intensive monitoring with a final rate

Table 1 Baseline and subsequent functional laboratory values.

Date	Hg (g/dL)/Hct (%) (14~18)/(42~52)	Platelets (130,000~400,000)	SCr (mg/dL) (0.5~1.4)	AST (U/L) (9~45)	ALT (IU/L) (17~63)	TBili (mg/dL) (0.2~1)
October 22, 2015	-	-	1.1	11	18	0.3
December 3, 2015	15/44.4	243,000	1.2	-	-	-
December 4, 2015	11.6/35.1	160,000	0.9	346	287	2.3
December 5, 2015	10.4/30.7	146,000	0.8	252	156	0.8
December 6, 2015	11.2/32.7	150,000	1	207	117	0.6
December 7, 2015	10.9/32.4	182,000	1	112	84	0.4
December 8, 2015	12.4/36.7	239,000	1	-	-	-
December 9, 2015	11.7/35.1	255,000	1	-	-	-

Hg: hemoglobin; Hct: hematocrit; SCr: serum creatinine; AST: aspartate aminotransferase; ALT: alanine aminotransferase; TBili: total bilirubin.

Table 2 PTT and INR laboratory monitoring.

Date	Time (h)	PTT (s) (21.2~31.3)	INR (2~3)	Infusion rate
October 22, 2015	1329	27.3	0.95	N/A
December 3, 2015	1030	24.7	0.98	2 mcg/kg/min (10.7 mL/h)
	1710	88.2	1.06	2 mcg/kg/min (10.7 mL/h)
	1910	80.2	1.91	2 mcg/kg/min (10.7 mL/h)
	2155	60.8	2.66	2 mcg/kg/min (10.7 mL/h)
December 4, 2015	100	58.3	2.69	2.25 mcg/kg/min (12 mL/h)
	500	59.4	2.94	2.25 mcg/kg/min (12 mL/h)
	1025	58.8	2.76	2.25 mcg/kg/min (12 mL/h)
	1530	50.2	1.81	2.5 mcg/kg/min (13.5 mL/h)
	2100	50.4	1.53	3 mcg/kg/min (16 mL/h)
December 5, 2015	200	53.4	1.67	3.5 mcg/kg/min (18.5 mL/h)
	555	57.4	2.04	3.5 mcg/kg/min (18.5 mL/h)
	1030	43.4	1.9	4.5 mcg/kg/min (24 mL/h)
	1400	47.4	2.05	5.5 mcg/kg/min (30 mL/h)
	1905	49.9	2.21	6.5 mcg/kg/min (35 mL/h)
	2355	51.6	2.27	7.5 mcg/kg/min (40 mL/h)
December 6, 2015	410	47.6	2.61	7.5 mcg/kg/min (40 mL/h)
	1030	68.8	3.18	7.5 mcg/kg/min (40 mL/h)
	1450	61.9	3.07	7.5 mcg/kg/min (40 mL/h)
December 7, 2015	500	65.4	3.18	7.5 mcg/kg/min (40 mL/h)

N/A: not applicable.

Table 3 Hematology laboratory results.

Date	Test	Result (reference range)
January 20, 2016	Platelets	310,000 (130,000~400,000)
	Homocysteine	16 μ mol/L (3.2~10.7)
	Albumin (electro)	4.8 g/dL (3.5~5.2)
	Alpha-1 globulin	0.2 g/dL (0.1~0.3)
	Alpha-2 globulin	0.8 g/dL (0.3~1.1)
	Beta globulin	1.1 g/dL (0.5~1.2)
	Gamma globulin	0.9 g/dL (0.6~1.5)
	Total protein (electro)	7.7 g/dL (6~8.2)
	Lactate dehydrogenase	208 IU/L (87~241)
	Erythrocyte sedimentation rate	20 mm/h (0~15)
	Reticulocyte count	1.27 % (0.51~1.81)
	M phospholipid Ab	< 10 PL Units (0~10)
	G phospholipid Ab	< 10 PL Units (0~10)
	A phospholipid Ab	< 10 PL Units (0~10)

of 7.5 mcg/kg/min (40 mL/h) being reached.

For discharge, the patient was bridged to warfarin using the factor Xa inhibitor fondaparinux 7.5 mg subcutaneously once daily with a goal INR of 2~3.

The patient was seen as an outpatient, after discharge, by hematology/oncology to rule out a malignancy or blood dyscrasias. Laboratory tests were ordered by

hematology/oncology to examine a potential cause for his arterial thrombi and observed heparin resistance, which included the following: homocysteine level, LDH (lactate dehydrogenase), ESR (erythrocyte sedimentation rate), SPEP (serum protein electrophoresis), anticardiolipin antibody, reticulocyte count, and a complete blood count with manual

differential. The patient was negative for anticardiolipins and the SPEP was normal (Table 3). Hematology/oncology determined that “no hematologic problem posing additional risk of thrombosis” was present and the recommendations were to continue antiplatelet therapy with ASA 81 mg PO daily and warfarin. The patient has been maintained on warfarin 42.5 mg per week taking warfarin 5 mg PO daily except warfarin 7.5 mg Monday, Wednesday and Friday for a goal INR of 2~3 for indefinite therapy without a recurring issue of lower extremity emboli.

3. Discussion

The patient was taken to the OR for emergent surgery due to multiple occlusive emboli of the right lower extremity. The patient is a smoker but has no known history of familial thrombophilia. This was a unique patient case that required a higher than normal argatroban infusion rate to maintain the PTT in a therapeutic window. The patient exhibited heparin resistance while in the OR having continued clot propagation despite a measured PTT of 117.8 s while on a therapeutic heparin infusion. Literature suggests that an antithrombin III deficiency may play a role in heparin resistance; however the patient did not have a baseline elevation in his PTT, which is seen quite frequently in heparin resistance. On occasion, the presence of lupus anticoagulant may cause the ACT to remain unaltered despite heparin use, yet this patient had a negative anticardiolipin workup [2].

Argatroban is indicated for HIT and PCI, with drastically different infusion rates and monitoring parameters based on indication. In HIT, argatroban is commenced at a standard rate of 2 mcg/kg/min unless precluding reasons are present, such as sepsis or hepatic failure, in which a lower starting dose is warranted. The PTT should be monitored every 2~4 h (longer interval for poor hepatic function) with adjustments being made based on the goal PTT. However, argatroban dosing in PCI requires a starting IV bolus followed by infusion rates 15~30 mcg/kg/min

with frequent monitoring of the ACT during the procedure to guide the infusion rate. For post-PCI anticoagulation, argatroban should be continued at a rate of 2 mcg/kg/min with monitoring of PTT for rate changes [4]. Patients with elevated liver enzymes and decreased hepatic function tend to be hyper-responsive to small changes in argatroban infusion rates [6]. Yet, despite the elevation in his LFTs found after initiation of argatroban, noted in Table 1, the patient still required escalated argatroban doses to achieve a therapeutic PTT.

4. Conclusions

This unique case documents an atypically high-dose argatroban infusion following observed heparin resistance highlighting a need for clinician awareness of this infrequently used anticoagulant. Presently, the patient has been controlled, without incident, on warfarin and aspirin therapies as an outpatient. Though no concrete explanation has been found, dissemination of this case will aid to educate and assist providers in improving patient safety and outcomes in the future for this high-risk medication.

Conflicts of interest

There is no conflict of interest.

Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or the position of the United States Government or the Department of Veterans Affairs.

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