Minimal prolongation of prothrombin time with extended exposure to argatroban

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Abstract

In the setting of acute heparin-induced thrombocytopenia (HIT), argatroban is one of the initial anticoagulants of choice, which is eventually bridged to warfarin over a period of 5 or more days. Argatroban prolongs prothrombin time (PT) and increases international normalized ratio (INR). However, the effects of prolonged argatroban exposure on the PT and INR are not known. We describe an unusual case of prolonged argatroban treatment in a patient with heparin-induced thrombocytopenia with thrombosis syndrome (HITTS) resulting in a minimal elevation of the INR. The patient received a total of 58 days of argatroban and was resistant to warfarin therapy, requiring a 13-day bridge to achieve a therapeutic INR of 2.0 to 3.0. Ultimately, argatroban was successfully transitioned to warfarin therapy when the INR was 2.7 on both agents, producing the confirmatory true INR of 2.4. Argatroban and warfarin co-therapy did not increase the INR beyond 4.0 after prolonged argatroban exposure. Clinicians should consider this unusual response in other cases of prolonged argatroban use, and monitor INR carefully during warfarin and argatroban co-therapy. The use of other methods to monitor anticoagulant therapy, such as chromogenic factor X assay (CFX), may be helpful in this setting.
Introduction

Heparin-induced thrombocytopenia (HIT) is a drug reaction that results from the production of heparin-platelet factor 4 (PF4) complex antibodies, which ultimately results in the activation of platelets and triggering of a cascade of pro-thrombotic events\(^1\). This cascade results in thrombocytopenia and can lead to venous or arterial thrombosis. A venous or arterial thrombosis event that occurs in a patient treated with heparin is referred to as heparin-induced thrombocytopenia with thrombosis syndrome (HITTS). HIT is diagnosed by both clinical assessment and detection of PF4 complex antibodies by laboratory assays, such as PF4 enzyme-linked immunosorbent assay (PF4-ELISA). Clinical assessment includes the degree and timing of thrombocytopenia, presence or suspicion of thrombosis, and other causes of thrombocytopenia. The American College of Chest Physicians Evidence-Based Clinical Practice Guidelines for treatment and prevention of heparin-induced thrombocytopenia recommend treatment of HITTS with either a direct thrombin inhibitor (DTI) or an indirect factor Xa inhibitor\(^2\).

Argatroban is a highly selective DTI that binds to clot-bound, fibrin-bound, and free thrombin and inhibits both platelet aggregation and production of thromboxane\(^3\). Argatroban is expected to prolong the activated partial thromboplastin time (aPTT) in a dose-dependent manner,\(^3\) and it is recommended to target a goal aPTT of 1.5 to 3 times the baseline\(^4,5\).

Current practice guidelines recommend initiation of a vitamin K antagonist once platelets have adequately recovered (typically >150 x 10\(^9\)/L) with overlap of argatroban for a minimum of 5 days\(^2\). However, argatroban also elevates the international normalized ratio (INR), complicating the bridging process. A goal INR of greater than 4.0 is generally accepted as therapeutic when argatroban and warfarin are administered concurrently\(^6\). It is recommended to hold argatroban and measure an INR 4 to 6 hours later in patients with normal hepatic function\(^3\). The available data for bridging from argatroban to warfarin comes from studies conducted in patients requiring only short-term argatroban therapy.
The purpose of this case report is to describe challenges associated with transitioning from argatroban to warfarin therapy for HITTS after a surgical procedure. The difficulty in this case stems from the minimal increase in INR when transitioning to warfarin in the setting of prolonged argatroban use.

Case Presentation

A 56-year-old African-American female diagnosed with left oral mandibular and buccal squamous cell carcinoma presented for tracheotomy, mandible resection, left neck dissection, mandibular maxillary fixation, and placement of mandibular reconstruction plate. Her past medical history was significant for type 2 diabetes, hyperlipidemia, and hypertension. She had a 10-year history of smoking, but no history of alcohol or illicit drug abuse. Medications prior to admission included aspirin 81 mg daily, atorvastatin 40 mg daily, glipizide extended-release 10 mg daily, lisinopril 20 mg daily, and metformin 1000 mg twice daily. The patient had no known drug allergies. Pertinent baseline laboratory values at admission were serum creatinine 0.7 mg/dL, platelet count 507 x 10^9/L, PT 15.1 sec, INR 1.2, and aPTT 30.3 sec.

The patient underwent surgical removal of the squamous cell carcinoma on hospital day 1. A continuous infusion of unfractionated heparin was initiated at 500 units/hour postoperatively for thromboprophylaxis. On hospital day 5, the heparin drip was transitioned to 5,000 units subcutaneously every 8 hours. The patient’s hospital course was complicated by operative site infection and aspiration pneumonia, which required a 14-day course of broad-spectrum antibiotics. On hospital day 9, physicians placed a peripherally inserted central catheter (PICC) line into the patient’s right basilic vein for anticipation of outpatient administration of intravenous piperacillin-tazobactam to complete the course of antibiotic therapy. The following morning, the patient complained of a swollen right hand and arm. With concern for possible compartment syndrome, a duplex scan was performed, which showed acute right upper extremity deep vein thromboses (DVTs) involving one of two brachial veins, the axillary vein, and the right distal subclavian vein. The PICC line was subsequently removed. Around the same time, the patient’s platelets dropped from 203 x 10^9/L on day 9 to 54 x 10^9/L on day 10. She received
the last dose of subcutaneous heparin in the morning on hospital day 10. Given the >50% reduction in platelet count that occurred 8 days after initiation of postoperative heparin, HIT was highly suspected especially in the setting of new DVTs. To confirm the diagnosis of HIT, PF4-ELISA, an antigen assay used to detect PF4 complex antibodies, was ordered, and an argatroban drip was initiated. Argatroban was initiated at a lower dose of 0.5 mcg/kg/min given the patient’s critical condition (i.e., severe sepsis and elevated liver enzymes [aspartate transaminase of 170 units/L, alanine transaminase of 119 units/L, and total bilirubin of 0.6 mmol/L]) with a goal aPTT of 60 to 80 seconds per hematology consult recommendation. On day 11, the patient was taken to the operating room for debridement of the left neck and facial wound and fasciotomy of the right upper extremity for right arm compartment syndrome. Catheter-directed thrombolysis using alteplase was also performed at this time. On day 11, the platelet count dropped to a nadir of 33 x 10^9/L. On day 12, the PF4-ELISA results revealed an optical density (OD) of 3.16 (the positive threshold is 0.40 OD), thus confirming the diagnosis of HIT.

The patient’s hospital course was further complicated by multiple visits to the operating room for insertion of inferior vena cava filter, debridement of mandible and fasciotomy sites, a necrotic right forearm requiring amputation of right distal 1st, 2nd, and 3rd fingers, split thick skin graft, and reconstruction of facial free flap. Persistent surgical site infection and new bilateral lower extremity DVTs likely related to intermittently holding argatroban for procedures also complicated her hospital course. She was maintained on argatroban alone with a goal aPTT of 60 to 80 seconds until hospital day 54 due to multiple surgeries and procedures requiring interruption of anticoagulation therapy. The INR ranged from 1.2 to 2.8 during this extended period, and the argatroban dose ranged from 0.5 to 2 mcg/kg/min. Her platelet count recovered to 152 x 10^9/L by day 16 and was fully recovered to levels between 400 x 10^9/L and 500 x10^9/L by day 33. On day 55, the otolaryngology and plastic surgery services determined the patient did not require further surgeries or procedures, and a bridge to warfarin was initiated.

On the day that warfarin 5 mg was initiated in conjunction with argatroban 2 mcg/kg/min, the INR and aPTT were 1.2 and 73.1 sec, respectively. The INR increased to 3.1 on day 58 and decreased to 2.0 on day 60, despite increasing the warfarin dose to 10 mg daily. During this period, no new medication was added or removed, and no change in diet occurred.
Concurrent medications at the time of initiation of warfarin included acetylcysteine nebulization, ascorbic acid, atorvastatin, bacitracin ointment, docusate, famotidine, hydrocodone-acetaminophen, hydromorphone, insulin aspart, insulin glargine, insulin NPH, ipratropium, metoprolol, multivitamin, nystatin powder, nystatin suspension, and zinc sulfate. The warfarin and argatroban doses and corresponding aPTT and INR values were tracked from hospital day 55 to day 68 (Table). The INR was 2.3 on day 61. Due to the INR fluctuation, argatroban was held for 6 hours; a repeat INR of 1.6 prompted immediate resumption of argatroban. The INR continued to fluctuate for the following 4 days, and a chromogenic factor X level was drawn on day 65 without holding argatroban, which came back at 74%. Because the therapeutic level is $\leq 45\%$, both argatroban and warfarin were continued. On day 68, the patient was transferred to the hematology-oncology service for initiation of chemotherapy. At this time, the INR was 2.7. Argatroban was held for 12 hours for port placement in preparation for administration of chemotherapy, and a repeat INR was therapeutic at 2.4. Argatroban was subsequently discontinued. The patient was discharged in stable condition after the first cycle of chemotherapy. To our knowledge, thromboembolism has not recurred.

Discussion

Argatroban directly inhibits thrombin and prolongs PT, both of which elevate INR. An INR level of $\geq 4.0$ is therapeutic while on warfarin and argatroban co-therapy\(^6-8\). An argatroban infusion can be discontinued and INR reassessed 4 to 6 hours later for the true INR on warfarin monotherapy\(^7\). In contrast, the presented case showed a minimal effect on PT and INR during bridging from argatroban to warfarin after extended exposure to argatroban. When our patient’s true INR was therapeutic at 2.4, the corresponding INR on co-therapy was only 2.7. There are several factors that may have contributed to the effect on PT and INR by argatroban.

One of the factors is the dose, or the corresponding plasma concentration, of argatroban. Several studies have investigated the relationship between argatroban dose and INR elevation. A study by Hursting et al. evaluated the effects of different argatroban concentrations on INR by adding the agent in vitro into plasma specimens obtained from 10 healthy donors and 35 patients on warfarin therapy. In this study, an increase in argatroban concentration increased the
sensitivity of combined INR to the warfarin INR. Sheth et al. also evaluated the effect of argatroban dose on INR on 24 healthy males. Linear relationships between combined INR and warfarin INR were derived at different argatroban doses, but this relationship was less predictable for higher doses (i.e., 3 or 4 mcg/kg/min). Gosselin et al. showed concentration-dependent effects on PT by three different direct thrombin inhibitors including argatroban. These authors concluded that PT and INR seemed to be affected most by therapeutic concentrations of argatroban. Taken together, these data suggest a dose-dependent relationship that is more predictable with argatroban doses < 2 mcg/kg/min. In practice, argatroban concentrations are not measured, and aPTT is considered to be a surrogate marker for therapeutic levels. A therapeutic aPTT level for the treatment of HIT is 1.5 to 3 times the baseline as shown by the ARG-911 and ARG-915 trials. In these multicenter, nonrandomized, historical-controlled, prospective trials, significantly fewer patients in the argatroban group than in the control groups reached the composite primary endpoint of all-cause death, all-cause amputation, and new thrombosis within 37 days of baseline. The mean argatroban doses in ARG-911 and ARG-915 were 2.0 ± 0.1 mcg/kg/min and 1.7 ± 1.0 mcg/kg/min, respectively.

Our patient’s argatroban dose was initiated at 0.5 mcg/kg/min and ranged from 0.4/mcg/kg/min to 2.0 mcg/kg/min. During co-therapy with warfarin, she received argatroban in doses of 1 to 2 mcg/kg/min, which is both consistent with original argatroban studies and within the predictable dose range. At the time of therapeutic INR, the argatroban dose was 1.3 mcg/kg/min. Although this is a relatively lower dose, our patient may have had decreased clearance of the drug given her complicated hospital course, which included severe sepsis. Thus, the argatroban dose may not have been the cause of the minimal elevation in INR.

Another factor that may influence the effect of argatroban is thromboplastin, which is the reagent used to measure PT. Thromboplastins have varying sensitivities to the depletion of coagulation factors and thus have different thromboplastin-specific international sensitivity index (ISI) assignments. Hursting et al. reported that a reagent with a lower ISI affects the INR to a lesser degree than one with a higher ISI when reagents with ISI of approximately 1.0 and 2.0 were compared. Sheth et al. found a linear relationship between warfarin monotherapy INR and co-therapy INR with various doses and ISI assignments, which was sensitive to both the
argatroban dose and the ISI for the thromboplastin used. The reagent used in our case was Neoplastine Plus with lot-specific ISI of 1.29. Sheth et al. reported that when using an argatroban dose of 2 mcg/kg/min and a reagent with ISI of 1.31, a measured INR of 4.0 would predict a true INR of 2.0, with a 95% confidence interval of 1.6 to 2.4. The coagulation laboratory in our institution confirmed there has been no change in the thromboplastin reagent used for many years, suggesting reagent sensitivity is unlikely the cause of minimal elevation in INR by argatroban in our patient.

Though the dose of argatroban and the thromboplastin reagent may not be implicated, one theory for this minimal elevation in INR is the setting of prolonged use in our patient. To our knowledge, there are no reports of similar experiences of minimal PT and INR elevation after prolonged argatroban use. When referring back to the initial trials of argatroban use in HIT patients, the duration of argatroban therapy was much shorter than in our patient. In ARG-911, the mean duration of therapy was 5.3 ± 0.3 days for the HIT arm and 5.9 ± 0.2 days for the HITTS arm. In ARG-915, the mean duration of therapy was 5.1 ± 4.2 days for the HIT arm and 7.1 ± 6.5 days for the HITTS arm. Additionally, one study that evaluated hospital-specific nomogram-based DTI management in patients with HIT reported 7.9 ± 8.7 days of DTI therapy. Our patient was maintained on argatroban for treatment of HIT for 45 days prior to the initiation of warfarin therapy. Once warfarin was initiated, argatroban was continued for additional 13 days, for a total of 58 days of therapy. Because there is little data available, it is difficult to know whether the duration of therapy caused the minimal elevation in INR in our patient, but it is a likely possibility given the above discussion.

Aside from withholding argatroban to measure a true INR, another option for measuring INR while on concurrent argatroban and warfarin therapy is the use of the CFX assay, which directly measures the percentage of enzymatic activity of factor X compared to normal function. Because argatroban only affects factor IIa, measuring the active factor X can be useful in determining the degree of effect of warfarin on the INR without the confounding effect of argatroban. One small study showed that a CFX ≤45% represents an INR of ≥2.0 with a sensitivity of 93%, a specificity of 78%, and an accuracy of 89%. Another small study confirmed the use of CFX assay with a sensitivity of 63.2%, a specificity of 80%, a positive
predictive value of 93.5, and a negative predictive value of 32.3\textsuperscript{13}. As shown in these studies, CFX of ≤45% can be interpreted as true INR of ≥2.0 while on both argatroban and warfarin. We measured CFX in our patient once during the bridging process, after it was apparent that the INR was not being inflated by argatroban. The measurement was taken on hospital day 65 after 10 doses of warfarin. At this time, the CFX was 74%, prompting us to further increase the dose of warfarin from 10 mg to 12.5 mg. The CFX assay is useful when the risk of thrombosis outweighs the benefit of ensuring a therapeutic INR level by holding argatroban for few hours. It is also useful when the assessment of elevation in INR by argatroban is difficult, such as in the presented case. In cases of prolonged exposure to argatroban, the risk of thrombosis may be relatively lower compared to short-term exposure, and thus withholding argatroban for 4 to 6 hours may be safe in order to assess the true INR value.

**Conclusion**

We do not fully understand the causes of our patient’s unexpected INR results in the setting of argatroban and warfarin co-therapy. The reasoning may be multifactorial and may include the duration of argatroban exposure and the sensitivity of the reagent used to measure PT. There is no current literature on prolonged use of argatroban therapy, so this is a possible area for future research. Clinicians should be aware of this potential effect on INR if they are managing a patient after prolonged argatroban use and assess the risk versus benefit of holding argatroban. Use of the CFX assay is worthy of consideration in patients with HIT.
References