Transitioning from Argatroban to Warfarin in Heparin-Induced Thrombocytopenia: An Analysis of Outcomes in Patients with Elevated International Normalized Ratio (INR)

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Abstract. Background: Heparin-induced thrombocytopenia (HIT) can lead to catastrophic thromboembolic complications and requires treatment with an alternative, rapidly active anticoagulant, such as a direct thrombin inhibitor (DTI), either to prevent or treat these complications. Switching to oral warfarin after initial treatment with a DTI is necessary in most patients. Most references related to warfarin suggest that an increased risk for bleeding will occur with elevated international normalized ratios (INRs) >4.6. In patients receiving argatroban, it is not uncommon to achieve an INR >4 during this transition. Because the clinical outcomes in patients achieving an INR >4 during combined argatroban/warfarin therapies for HIT are not well described, we evaluated the clinical outcomes of 111 patients with this phenomenon.

Methods: We identified patients from the prospective studies of argatroban anticoagulation, Argatroban-911 and Argatroban-915. Data collected from these studies included death from all causes, amputation, new thrombosis, major bleeding, INR values, argatroban doses, aPTT values, platelet counts, and duration of therapy.

Results: Patients were on argatroban monotherapy for a median of 2.8 (0.1–8.1) days, and on cotherapy for a median of 3.7 (0.9–12.8) days. The median platelet count was 70.9 (18–325) × 10^9/L at the time of HIT diagnosis and increased to 94 (30–324) × 10^9/L by the time warfarin was initiated. At a median argatroban dose of 1.4 (0.2–2.0) mcg/kg/min, the maximum INR ranged from 4.1 to 21.2 (median 6.4, n = 111) and the corresponding aPTT ranged from 48.1 to 105 (median 71, n = 93) seconds. After argatroban cessation, the first recorded INR within 4 to 24 hours ranged from 1.5 to 12.5 (median 2.9, n = 38). Adverse clinical outcomes occurred in 9 (8.1%) patients during cotherapy and in 12 (10.8%) patients after argatroban anticoagulation was discontinued. Adverse clinical outcomes included 7 cases of new thrombosis, 3 amputations, 12 deaths and 1 major bleed. Eleven of 12 (91.7%) patients died due to causes other than thrombosis, and most deaths (83%) occurred following cotherapy. Five (4.5%) patients developed new thrombosis despite an INR > 4. In contrast only 1 (0.9%) patient experienced major bleeding.

Conclusion: In patients receiving argatroban/warfarin cotherapy and with an elevated INR > 4, the risk for thrombosis exceeds the risk of bleeding. Traditional paradigms concerning elevated INRs and warfarin may need to be redesigned for the patient population on cotherapy with direct thrombin inhibitors.

Abbreviated Abstract. The clinical outcomes of 111 patients with INRs > 4 while on combined argatroban (dose ≤ 2 mcg/kg/min) and warfarin were evaluated. Adverse clinical outcomes (7 new thrombosis, 3 amputations, 12 deaths and 1 major bleed) occurred in 21 patients. Eleven deaths were due to causes other than thrombosis. Five patients developed new thrombosis while only 1 had major bleeding. The risk for thrombosis exceeds the risk of bleeding in patients with HIT despite an INR > 4.

Key Words. argatroban, warfarin, international normalized ratio (INR), heparin-induced thrombocytopenia

Introduction

Heparin-induced thrombocytopenia (HIT) is a severe, immune-related complication of heparin, often resulting in devastating thromboembolic outcomes. Approximately 1 to 5% of patients treated with heparin develop HIT, either with or without thrombosis [1,2]. Patients with isolated HIT (i.e., HIT without thrombosis) have a 19 to 52% risk for new thrombosis if heparin is discontinued and another parenteral anticoagulant is not used [3]. The mortality of HIT with thrombosis is reported to be as high as 20% to 30% [3,4]. Heparin should be discontinued immediately when HIT is suspected and an alternative anticoagulant initiated [3,5,6].

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Two direct thrombin inhibitors (DTIs), argatroban and lepirudin, have been shown in prospective multicenter trials to improve clinical outcomes in HIT [7–10]. Warfarin is not recommended initially in acute HIT due to its delayed onset of action [5,6] and its association with the development of venous limb gangrene and warfarin-induced skin necrosis [11–14]. Switching to warfarin is appropriate, however, in patients requiring prolonged anticoagulation therapy for an underlying medical condition or prophylaxis after recovering from active HIT. Current practice guidelines recommend initiating warfarin only after the patient has improved clinically, the patient is adequately anticoagulated with a DTI or other nonheparin anticoagulant, and the platelet count has recovered to at least 100 \( \times 10^9/L \) (preferably 150 \( \times 10^9/L \)). Warfarin should be overlapped with a DTI for at least 5 days, and the INR should also be in the accepted therapeutic range for at least 2 consecutive days before discontinuing the DTI [15].

DTIs are routinely monitored using the activated partial thromboplastin time (aPTT). They may also affect the prothrombin time and the international normalized ratio (INR), the laboratory measure used to monitor warfarin. Combined anticoagulation with a DTI and warfarin produces an INR response that is greater than observed with warfarin alone [16–19]. A study in healthy volunteers has shown that an INR > 4 in subjects receiving concurrent argatroban (\( \leq 2 \) mcg/kg/min) and warfarin generally reflects a therapeutic INR on warfarin alone [17]. Prescribing guidelines for transitioning from argatroban to warfarin recommend discontinuing argatroban when the cotherapy INR is above 4 (at argatroban doses \( \leq 2 \) mcg/kg/min), assuming an overlap of at least 5 days. The INR should then be repeated 4 to 6 hours later, when the anticoagulant effects of argatroban would be expected to be negligible, to ensure a therapeutic value on warfarin alone [17]. Although INRs >4 while on warfarin are historically associated with a significantly increased risk of bleeding [21,22], INRs >7 while on argatroban and warfarin cotherapy have been reported to occur without bleeding in both healthy subjects [17] and HIT patients [23]. However, the clinical outcomes in HIT patients achieving an INR >4 during combined argatroban \( \leq 2 \) mcg/kg/min and warfarin therapies are not well described.

We retrospectively evaluated the clinical outcomes of patients who had an INR >4 while on combined argatroban \( \leq 2 \) mcg/kg/min and warfarin therapy during the Argatroban-911 and Argatroban-915 prospective studies [9,10]. Although the prospective studies did not legislate the transition from argatroban to warfarin, the patients reported herein would have been considered eligible for argatroban discontinuation according to current guidelines.

**Methods**

**Patients and anticoagulant therapy**

We reviewed patient case records from the prospective, multicenter studies of argatroban anticoagulation in HIT [9,10] to identify patients who initiated warfarin while on argatroban and who achieved an INR >4 while on combined (dose \( \leq 2 \) mcg/kg/min) therapy. The prospective studies included patients who had a clinical diagnosis of HIT with or without thrombosis, and patients with a history of HIT currently requiring anticoagulation. HIT was defined as an unexplained \( \geq 50\% \) decrease in the platelet count from the patient’s baseline or an absolute decrease in the platelet count to \( < 100 \times 10^9/L \) on heparin therapy. The Institutional Review Board (IRB) at each participating center approved these studies, and written informed consent from patients was obtained.

Heparin was discontinued in all study participants who had a clinical diagnosis of HIT. Intravenous argatroban (GlaxoSmithKline, Philadelphia, PA), 2 mcg/kg/min, was initiated as a continuous infusion in patients with HIT and in patients with a history of HIT currently requiring anticoagulation. A lower dosage of argatroban was allowed if medically necessary (e.g. the presence of hepatic impairment). Dose adjustments, up to 10 mcg/kg/min, were made to maintain a aPTT 1.5 to 3 times the patients baseline aPTT but not to exceed 100 seconds. The aPTT was determined 2 hours after initiation of therapy, 2 hours after each dose adjustment and daily thereafter. Argatroban was continued until the underlying condition resolved, appropriate anticoagulation was provided with other agents, or for 14 days. Warfarin dosing and monitoring were managed independently by physician investigators without a specific protocol.

**Assessments**

During the prospective studies, patients were followed from baseline (the date argatroban was initiated), during treatment, and for 30 days after argatroban cessation. The data collected from case records included clinical events (i.e., death from all causes, amputation, new thrombosis and major bleeding), INR values, argatroban doses, aPTT values, platelet counts, and the duration of therapy. New thrombosis was identified clinically and documented objectively (by ventilation/perfusion scans or ultrasound examination) when clinically necessary. Physical examinations were routinely performed within 24 hours after argatroban cessation, at which time arterial and venous duplex doppler studies and ventilation/perfusion scans were also performed in the Argatroban-911 study. Major bleeding was defined as overt, and associated with a hemoglobin decrease \( \geq 2 \) g/dl, or that lead to a transfusion of \( \geq 2 \) units,