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# Argatroban for the Treatment of Heparin-Induced Thrombocytopenia in End Stage Renal Disease and Acute Kidney Injury

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## ABSTRACT

The diagnosis and treatment of heparin-induced thrombocytopenia (HIT) is difficult in any patient but, due to chronic exposure to heparin during dialysis, chronic risk for thrombosis and/or bleeding, and variable pharmacokinetics of medications, the management of HIT in patients with acute kidney injury (AKI) or end stage renal disease (ESRD) may be even more complex. The treatment of HIT requires therapeutic anticoagulation with a non-heparin based medication and most of these medications are renally eliminated, as well as somewhat, if not extensively, protein-bound. There is a lack of literature describing the treatment of HIT in patients with either ESRD or AKI, though the use of non-heparin derived anticoagulants during dialysis in an ESRD patient with HIT has been described. This report describes the use of argatroban, a direct thrombin inhibitor, for the treatment of HIT in two patients with ESRD and one patient with AKI.

## BACKGROUND

Heparin-induced thrombocytopenia (HIT) Type II is an antibody-mediated adverse drug event that can be life-threatening if not diagnosed and treated quickly and aggressively.<sup>1-2</sup> Unfortunately, HIT can be difficult to diagnose and diagnosis requires both clinical and laboratory confirmation.<sup>3</sup> While algorithms have been used to help confirm HIT, the more recent 4-T score was developed and validated to help differentiate between patients with HIT and patients with thrombocytopenia from another cause (Table 1).<sup>4</sup> The first “T” is thrombocytopenia. Patients with HIT typically have a fall in platelets 50% or more from baseline and may have a low platelet value (less than 100 k/mm<sup>3</sup>-150 k/mm<sup>3</sup>). The second “T” is timing. HIT-associated thrombocytopenia usually presents about five-to-10 days following a naïve exposure to heparin, but may present rapidly (within hours) if the patient had a recent exposure. The third “T” is thrombosis. About half of patients with HIT have thrombotic complications and the risk of thrombosis remains high, even after platelet rebound. The fourth “T” is other causes of thrombocytopenia, all of which must be excluded to rule in the diagnosis of HIT. If the patient has a high clinical suspicion of HIT as evidenced by a high 4-T score, then a laboratory test should be performed to confirm the diagnosis. Laboratory tests used to diagnose HIT include the PF-4 heparin antibody test, the functional assays, and the serotonin release assay. However, these tests are not always readily available and empiric treatment may be necessary in the absence of laboratory data.

The diagnosis of HIT in patients with end stage renal disease (ESRD) can be even more difficult. Patients with ESRD often have a chronic exposure to heparin as a standard part of dialysis, complicating the “timing” aspect of the 4-T score. Patients with ESRD also may have a baseline-elevated risk for either thrombosis or bleeding, which complicates the “thrombosis” aspect of the 4-T score.<sup>5</sup>

The management of HIT requires the cessation of all heparin-containing products and therapeutic anticoagulation to prevent and/or treat thrombosis with either a direct thrombin inhibitor or an anti-factor Xa therapy.<sup>6</sup> Unfortunately for the patient with ESRD or AKI, the majority of available treatments, including the direct thrombin inhibitor bivalirudin (Angiomax,<sup>®</sup> The Medicines Company) and the anti-factor Xa therapy fondaparinux (Arixtra,<sup>®</sup> GlaxoSmithKline) are either in part or entirely renally excreted,<sup>3,7,8</sup> and fondaparinux is also extensively bound to plasma proteins.<sup>7</sup> Argatroban (Argatroban,<sup>®</sup> GlaxoSmithKline) can provide therapeutic anticoagulation, is primarily hepatically cleared and is only 20-percent bound to plasma albumin, therefore making it an attractive option in treating HIT in patients with ESRD or AKI.<sup>9</sup>

Argatroban is a synthetic direct thrombin inhibitor that reversibly binds to the thrombin active site. It is metabolized in the liver and primarily excreted in the feces. Argatroban does not require dosage adjustment in patients with renal impairment; however, about 16-23 percent of the argatroban dose is excreted unchanged in the urine. Studies have shown that 20 percent of argatroban is estimated to be removed during a four-hour hemodialysis session and that activated clotting times fall during dialysis sessions, with intradialytic clearance of argatroban estimated to be between 0.2-0.7 ml/min/kg.<sup>9-10</sup> There are currently no recommendations on the clinical significance of the fall in clotting times, or on whether the dose of argatroban should be increased to compensate for the reduction in the anticoagulant effect during dialysis.

When compared to patients with normal renal function, argatroban steady-state concentrations appear not to be changed (1,236 ng/mL for patients with clearance creatinine (CLcr)>80 mL/min versus 1,253 ng/mL for patients with CLcr between 0-29 mL/min) but systemic clearance is reduced, thereby increasing half-life and area under the curve (4.6 mL/kg/min, 47 min, and 4,788 ng\*h/mL for patients with CLcr >80 mL/min, respectively, versus 3.4 mL/kg/min, 64 min, 5,874 ng\*h/mL in patients with CLcr between 0-29 mL/min, respectively).<sup>10</sup> Despite alterations in pharmacokinetic parameters, activated partial thromboplastin time (aPTT) and activated clotting time (ACT) appear to be unchanged (61 (54-76) sec and 208 (192-286) sec for patients with CLcr >80 mL/min, respectively, and 62 (52-86) sec and 233 (203-277) sec for patients with CLcr between 0-29 mL/min, respectively).<sup>10</sup>

The use of argatroban has been previously described for intradialytic use in the patient with HIT,<sup>11-12</sup> as well as for the treatment of HIT in patients on CRRT.<sup>13</sup> Here we describe the use of argatroban for the treatment of suspected HIT in two patients with ESRD and one patient with AKI.

## CASE REPORTS

### Case 1

The first patient is a 53-year-old, 63 kg Caucasian female with end stage renal disease on hemodialysis who was admitted to our institution for sepsis, respiratory failure, altered mental status and a missed dialysis session. Her past medical history includes a cerebrovascular accident and subsequent seizures, mitral valve replacement on chronic warfarin, recurrent urinary tract infections, and tobacco abuse. Her surgical history includes several failed arteriovenous fistulas.

Upon admission she was noted to meet all four systemic inflammatory response syndrome criteria (SIRS) and was broadly covered with antibiotics. She received continuous renal replacement therapy throughout much of her hospital stay but was able to transition back to intermittent hemodialysis upon discharge. She had a complicated 63-day hospital course, including seizures, multiple intubations/extubations, multiple invasive line changes, parenteral nutrition therapy, continuous renal replacement therapy, *Aspergillus fumigatus* pneumonia, *Escherichia coli* urinary tract infection, *Candida tropicalis* fungemia, methicillin sensitive *Staphylococcus aureus* bacteremia, lactic acidosis, and a softball-sized false aneurysm that required emergent surgery.

On hospital day 47, the patient's platelets had fallen from 324 k/mm<sup>3</sup> on hospital day 43 to a nadir of 75 k/mm<sup>3</sup> following a 39-day exposure to therapeutic heparin infusion. Of note, she was empirically treated with linezolid on hospital days three-20 and again on hospital days 38-41. On hospital day 47, she was initiated on argatroban at a dose of 2 mcg/kg/min. The patient's first aPTT was greater than 200 so the dose was held and reduced. This dose had to be reduced to a low of 0.3 mcg/kg/min for five days, but then subsequently had to be increased to the original 2 mcg/kg/min dose to achieve therapeutic aPTT levels. Argatroban was continued until her platelets recovered to 501 k/mm<sup>3</sup> on hospital day 56. She had a platelet factor of 4-heparin antibodies (PF4-heparin antibodies) on hospital day 47, which equaled 7% (where <20% is deemed negative). At the end of hospitalization, the patient was transferred to outpatient rehabilitation. This patient and each subsequent patient's 4T scores are presented in Table 2.

## Case 2

Patient two is a 73-year-old, 71 kg Caucasian male with end stage renal disease on hemodialysis, with severe microvascular complications secondary to Type II diabetes mellitus, who was admitted for a small bowel obstruction. Pertinent past medical history includes coronary catheterization with stenting, history of peritoneal dialysis (discontinued secondary to peritonitis), peripheral artery disease, and multiple chronic wounds, some of them gangrenous, on hands, feet, and penis.

During his 25-day hospital course, he required a left upper extremity fistulogram, partial penectomy, parenteral nutrition therapy, and had hypotension requiring vasopressors. The patient received dialysis three-times-weekly throughout his hospital stay, though some dialysis sessions were held due to hypotension.

On hospital day ten, the patient's platelets had fallen from 168 k/mm<sup>3</sup> on hospital day three to 119 k/mm<sup>3</sup> following a nine-day exposure to prophylactic heparin (5,000 units subcutaneously every eight hours). When platelets rebounded following discontinuation of heparin on hospital day 11, heparin induced thrombocytopenia was presumed and argatroban was started at a dose of 2 mcg/kg/min and was continued through hospital day 18, when a therapeutic INR was achieved with warfarin and argatroban was discontinued. The patient's platelets reached a nadir of 106 k/mm<sup>3</sup> on hospital day 14 while on argatroban. He had a PF4-heparin antibody test on hospital day 10 which equaled 23 percent. Following hospitalization, the patient was transferred to the nursing home.

## Case 3

Patient three is a 66-year-old, 58 kg Caucasian female admitted to the hospital for a left-sided cerebrovascular accident possibly due to a thrombotic complication of culture negative endocarditis. She was admitted three days after a previous hospitalization for culture negative endocarditis, where she was treated with prophylactic heparin (5,000 units subcutaneously every eight hours).

On hospital day eight, the patient's serum creatinine began to rise from a baseline of 0.4-0.5 mg/dL to 0.73 mg/dL and continued to rise to a high of 4.32 mg/dL on hospital day 13. On hospital day nine, the patient's platelets substantially declined from 322 k/mm<sup>3</sup> on hospital day six to 42 k/mm<sup>3</sup>. Argatroban was initiated at a dose of 2 mcg/kg/min and was continued until hospital day 12, when lung cancer with metastases was noted and the patient was transitioned to end-of-life care. On hospital day nine she had a platelet PF4-heparin antibody test which was 35 percent. The patient did not receive dialysis and further HIT work-up was not done.

## DISCUSSION

In this report, we describe the treatment of presumptive HIT in two patients with ESRD receiving hemodialysis and in one patient with AKI. In two patients, the dosage recommended by the package insert provided therapeutic anticoagulation without overcoagulation. However, one patient required several dosage adjustments throughout the course of argatroban therapy. Specifically when patient one was initiated on argatroban at the dose recommended by the package insert, within two hours the PTT was >200 msec. Subsequently, the dose of argatroban was reduced. Over time, the patient's PTT decreased to the subtherapeutic range and the argatroban dose was gradually increased to the rate recommended by the package insert.

While there have been a few case reports regarding argatroban in this patient population, the literature is not clear-cut in the management of these patients. Most of the literature describes argatroban with continuous renal replacement therapy (CRRT) instead of conventional hemodialysis, as we describe in two of our patients. In one case report, a 37-year-old patient admitted for emergency bowel resection developed acute kidney injury and received continuous veno-venous hemofiltration.<sup>14</sup> The patient received argatroban for suspected HIT and thrombosis at an initial rate of 0.5 mcg/kg/min,

which required reduction due to overanticoagulation. Throughout the patient's course, the patient required a dosage of 0.8 mcg/kg/min for 23 consecutive days until transitioned to a vitamin K antagonist.<sup>14</sup>

Reddy, et al., retrospectively described 47 patients with HIT requiring renal replacement therapy who received argatroban at a starting dose of 2 mcg/kg/min.<sup>15</sup> In the patients without hepatic impairment, the median infusion dose was 1.7 (0.2-2.8) mcg/kg/min. The median aPTT was 2.2 (1.6-3.6) relative to baseline.<sup>15</sup> Few patients experienced major bleeding.

Another study describes 30 patients with HIT type II receiving CRRT. The study authors utilized several critical illness severity scores to predict patients who may require reduced doses of argatroban while receiving CRRT.<sup>12</sup>

## CONCLUSION

Our three case reports show that patients with ESRD and AKI may be safely and effectively treated with argatroban; however, the degree of anticoagulation provided at a given dose may vary among patients and may change throughout the course of therapy.

It is our conclusion that argatroban is an option for the treatment of HIT in patients with ESRD and AKI but that extra vigilance must be used to ensure appropriate anticoagulation while preventing suprathreshold anticoagulation.

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<b>Table 1. 4-T score for the diagnosis of HIT.<sup>4</sup></b>			
	2 points	1 point	0 point
Thrombocytopenia	>50% fall in platelet count and nadir <20	30-50% fall in platelet count and nadir 10-19	<30% fall in platelets and nadir <10
Timing	Clear onset between 5-10 days following exposure or <1 day if previous heparin exposure	Consistent with 5-10 day fall in platelets, but unclear, greater than 10 days, or fall <1 days without previous exposure	
Thrombosis	New confirmed thrombosis, skin necrosis, or acute systemic reaction	Progressive or recurrent thrombosis, non-necrotizing skin lesions, suspected thrombosis	None
Other causes of thrombocytopenia	None	Possible	Definite

<b>Table 2. 4-T Score and laboratory test results for patients in this study.</b>			
Patient	1	2	3
Thrombocytopenia	2	0	2
Timing	1	2	2
Thrombosis	0	0	1
Other causes of thrombocytopenia	1	2	2
Total 4-T score	4	4	7
PF-4 (<20% is negative)	7%	23%	35%