Evaluation of an Argatroban Nomogram for Heparin-Induced Thrombocytopenia

Alexandra Centeno, PharmD; Marta Miyares, PharmD, BCPS; Ennie Cano, PharmD, BCPS
Jackson Memorial Hospital Department of Pharmacy, Miami, FL

Background

Heparin-induced thrombocytopenia (HIT) is an antibody-mediated adverse effect of heparin that is associated with a high risk of venous and arterial thrombosis. Although HIT can present as isolated thrombocytopenia, it may be associated with the development of thrombotic events. Consequently, early discontinuation of heparin and initiation of alternative anticoagulants such as direct thrombin inhibitors (i.e., argatroban, lepirudin, bivalirudin) and factor Xa inhibitors (i.e., fondaparinux) are necessary for the prevention and treatment of HIT and HIT with thrombosis (HITT).[1] It became increasingly important that development of a protocol was essential to help reduce the patient's risk for bleeding and thrombotic complications. An argatroban (ARG) nomogram was developed with 2 titration variations, the first of which was a standard titration scale. The second titration option was designed for critically-ill, hepatic dysfunction, heart failure or recent cardiac surgical patients. This alternative was based on literature and consensus treatment guidelines suggesting excessive anticoagulation with FDA approved doses.[2-5] Additionally, we incorporated recommendations on how to transition patients to warfarin with the use of argatroban or fondaparinux (FONDA).

Objectives

To evaluate clinical and laboratory outcomes of an argatroban nomogram in patients with confirmed or suspected heparin-induced thrombocytopenia

- Percentage of patients with therapeutic, supratherapeutic and subtherapeutic aPTT at predetermined time intervals
- Average time to stabilization and number of dose adjustments
- Secondary analysis of criticially-ill population and those receiving fondaparinux

Methods

Design

- Retrospective cohort study at a large tertiary teaching hospital from January to December 2009

Data Collection

- Computerized database system and medical charts from inpatient admissions
  - Baseline demographics, laboratory values, anticoagulation medication history, diagnostic procedures related to assessment of bleeding or thrombosis

Statistical Analysis

- Performed utilizing PASW with p< 0.05 signifying significance
- Fisher's exact or Chi-square test were utilized to compare categorical variables
- Student's t-test or Mann-Whitney U-test were utilized to compare continuous variables

Inclusion Criteria

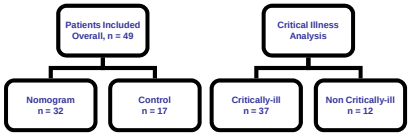
- Adult patients (≥ 17 yr) who required argatroban treatment for at least 24 hours for suspected or confirmed HIT

Exclusion Criteria

- Pediatric patients, those receiving argatroban for percutaneous coronary intervention or coronary artery bypass grafting, or on argatroban for reasons other than HIT

Methods

Figure 1. Subject Stratification



Nomogram Protocol (abbreviated)

Table 1. Argatroban Sliding Scale

PTT	1 mcg/kg/min (Usual dose)	0.5 mcg/kg/min* (Reduced Dose)
< 35	↑ by 0.5 mcg/kg/min	↑ by 0.3 mcg/kg/min
35 to 44	↑ by 0.3 mcg/kg/min	↑ by 0.1 mcg/kg/min
45 to 80 (goal)	No Change	No Change
81 to 90	↓ by 0.3 mcg/kg/min	↓ by 0.1 mcg/kg/min
> 90	Hold infusion x 1hr, then ↓ by 0.5 mcg/kg/min	Hold infusion x 1hr, then ↓ by 0.3 mcg/kg/min

*For patients with hepatic dysfunction, heart failure, multiple organ failure, severe anasarca, recent cardiac surgery and critically-ill patients a reduced dose of 0.5 mcg/kg/min was recommended.

Results

Table 2. Demographic and Baseline Characteristics

Variables, n (%)[a] unless otherwise specified	Nomogram (n=32)	Control (n=17)
Mean age, yr (mean ± std.dev)	55 ± 17	62 ± 15
Gender, male	19 (59.4%)	9 (52.9%)
Weight, kg (mean ± std.dev)	82.5 ± 27.5	67.0 ± 15.2
Nº Critically-ill (location)	24 (75%)	13 (76.5%)
Mean length of stay, days	20 ± 14	29 ± 24
Nº SRA ordered	6 (18.8%)	1 (5.9%)
Total PF4 ordered	20 (62.5%)	15 (70.6%)
PF4 positive	10 (40%)	5 (33%)
PF4 result not available	7	2
PF4 Level (mean Optical Density)	0.77	1.16
History of HIT	5 (15.6%)	2 (11.8%)
HIT confirmed	12 (37.5%)	5 (29.4%)
On Renal Replacement Therapy	14 (43.8%)	5 (29.4%)
Marker of critical illness[b]	24 (75%)	14 (82.4%)
Hepatic Dysfunction	4 (15.4%)	3 (17.6%)
Total Bilirubin (mean ± std.dev)	0.8 ± 0.8	2.4 ± 3.8

[a] All demographic variables were p = ns between treatment groups
[b] Marker of critical illness defined as having any of the following: hepatic dysfunction, heart failure, multiple organ failure, or critically-ill (clinical).

Results

Figure 2. Overall Maintenance Argatroban Dose

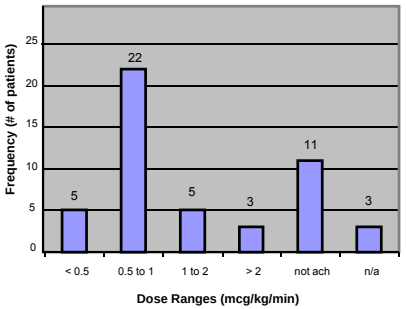


Table 3. Overall Outcomes

Outcomes, n (%)	Nomogram (n=32)	Control (n=17)	p
Median *initial* ARG dose (mcg/kg/min)	0.50	1.30	0.04
Median *maintenance* ARG dose[a] (mcg/kg/min)	0.60	0.75	0.86
Mean time to dose stabilization (hr)	15.4	12.4	0.64
Nº of dose adjustments to reach maintenance dose	1.4	0.4	0.08
Therapeutic aPTT at 24hr	21 (79%)	8 (62%)	0.47
Supratherautic aPTT at 24hr	3 (11%)	5 (38%)	0.08

[a] Maintenance dose defined as two consecutive aPTTs within therapeutic range.

Table 4. Major Bleeding and Thrombotic Events Overall Analysis

Clinical Event	Nomogram	Control	p value
Major Bleeding	1	2	0.27
Minor Bleeding	4	2	1.00
Thrombosis	2	0	0.53

Results

Table 5. Secondary Analysis

Outcomes	Overall
Median maintenance[a] ARG dose in critically-ill subgroup	0.5 mcg/kg/min
Fondaparinux to warfarin overlap	2.6 days

Critically-Ill Subgroup (n=37)	Nomogram[b]	Control[b]
Therapeutic aPTT at 24hr	16	5
Supratherautic aPTT at 24hr[c]	2	5

[a] Maintenance dose defined as two consecutive aPTTs within therapeutic range.
[b] Comparison based on reduced n; excluding aPTTs not available or where argatroban had been discontinued, at 24 hr.
[c] p value < 0.05, in critically-ill population, nomogram vs control comparison.

Table 6. Adverse Events in Secondary Analysis

Clinical Event	Critically-Ill	Non Critically-Ill	FONDA
Major Bleeding	3	0	0
Minor Bleeding	6	0	0
Thrombosis	2	0	0

Conclusions

- Our study demonstrates the usefulness of a weight-based argatroban dosing nomogram that rapidly achieves and maintains therapeutic levels and prevents excessive anticoagulation.
- Though more dose adjustments were needed in the nomogram group, the median time to dose stabilization was similar for both groups. Consequently, the incremental dose adjustment in critically ill patients was modified to 0.3 mcg/kg/min.
- All documented adverse events occurred in the critically-ill population.
- This is a retrospective study with a small sample size. Prospective studies to validate these findings are warranted.

References

1. Linkins LA, Dans AL, Moores LK, et al. Treatment and Prevention of Heparin- induced Thrombocytopenia Antithrombotic therapy and prevention on thrombosis, 9th ed : American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141(2)(Suppl):e95S-e530S.
2. Ansara AA, Arif S, Warhurst RD. Weight-Based Argatroban Dosing Nomogram for Treatment of Heparin-Induced Thrombocytopenia. Ann Pharmacother 2009;43:9-18.
3. Koeber J. An Evaluation of an Argatroban Dose Titration Nomogram (abstract). J Thromb and Haemost 2007; 5 Supplement 2: P-M-649.
4. Reichert MG, MacGregor DA, Kincaid EH, Dolinski SY. Excessive Argatroban Anticoagulation for Heparin-Induced Thrombocytopenia. Ann Pharmacother 2003;37:652-4.
5. Swan SK, Hursting MJ. The Pharmacokinetics and Pharmacodynamics of Argatroban: Effects of Age, Gender, and Hepatic or Renal Dysfunction. Pharmacotherapy 2000;20:318-29.

Contact Information

Alexandra Centeno, PharmD
Jackson Memorial Hospital
Pharmacy Administration
1611 NW 12th Avenue
Miami, FL 33136-1096
Email: alexandra.centeno@jhsmiami.org
Authors have no conflicts of interest to disclose