Evaluation of the Transition Process from Argatroban to Warfarin in Heparin Induced Thrombocytopenia

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Background

- Heparin-induced thrombocytopenia (HIT) is an immune-mediated reaction which increases the risk of thrombosis
- Argatroban, a parenteral direct thrombin inhibitor, is often used for initial HIT treatment before transitioning to an oral agent
- Argatroban produces a dose-dependent “false” INR elevation which complicates the bridge to warfarin
- Our health system provides guidelines for this bridge:
  - Initiate warfarin when platelet count has returned to baseline or ≥ 150 x 10^9/L
  - Start warfarin at doses ≤ 5 mg
  - INR prior to warfarin bridge
  - Overlap for a minimum of 5 days
  - INR goal on co-therapy is ≥ 4
  - Hold argatroban and check a true INR (warfarin monotherapy INR) in 4-6 hours
  - Two-step process for argatroban doses > 2 mcg/kg/min where a co-therapy INR is checked on a reduced argatroban dose of 2 mcg/kg/min prior to a true INR check
  - Correct argatroban action upon INR check
- Evaluation of the transition from argatroban to warfarin is limited

Objectives

- Evaluate compliance with institutional argatroban to warfarin bridging guidelines
- Evaluate success of the transition from argatroban to warfarin

Methods

- Single-center, retrospective observational cohort study of patients admitted between January 2019 and June 2024
- Adult patients with positive HIT serology who received argatroban and warfarin with the intent to transition to warfarin
- Bridge courses were not fully assessed if stopped early
- Data collected included demographics, anticoagulant dosing, HIT serology, bleeding, thrombosis & relevant laboratory values
- Bleeding and thrombosis were assessed from initiation of warfarin to 24-hours post argatroban discontinuation and 30-days post bridge initiation, respectively
- Primary endpoint: compliance with institution guidelines for bridge process (assessment of up to 8 items) requires compliance in all areas to be designated as compliant
- Secondary endpoints: transition success, bleeding & thrombosis
- Transition Success: completed within 7-days, INR monotherapy of 2.0 – 3.5, for next 2 morning INR checks, no bleeding, thrombosis, or argatroban restarts within 5 days for a low INR
- Descriptive statistics, Fisher’s Exact test, p < .05 was statistically significant

RESULTS

Table 1: Baseline and Patient Characteristics (n=29)

Characteristic	Result
Male Gender, n (%)	12 (41.4)
Age (yrs), mean ± SD	60.9 ± 18.2
Weight (kg), mean ± SD	107 ± 33.6
Patient Type (surgical/medical), n/n	19/10
Presence of liver disease, n (%)	2/29 (6.9)
HIT Classification: Isolated HIT, n (%) HIT with thrombosis, n (%)	 9 (31) 20 (69)
Heparin Platelet Factor 4 Antibody Positive, n (%)	29 (100%)
Heparin Platelet Factor 4 Optical Density, mean ± SD	2.4 ± 0.44
Serotonin Release Assay (n=22): Positive, n Borderline/Indeterminate, n	 20 2

Table 2: Overview of Argatroban Therapy

Characteristic	Result
Patients with multiple bridge courses, n (%)	3 (10.7)
Highest INR on argatroban alone (n=23), mean ± SD	2.3 ± 0.7
Argatroban duration of therapy (days), mean ± SD	14.8 ± 9.5
Day of argatroban therapy when warfarin was initiated, median (range)	8 (1-44)
Days of co-administration, mean ± SD	5.2 ± 2.7
Argatroban dose*, (mcg/kg/min), mean ± SD	2.6 ± 1.9
Patients with one step transition, n (%)	15 (51.7)
Patients requiring & undergoing two-step transition, n (%)	8 (27.6)
Patients requiring but NOT undergoing two-step transition, n (%)	6 (20.7)
Change in INR after argatroban discontinued, mean ± SD	-1.41 ± 0.9
Documented increased length of stay for bridge, n (%)	7 (24.1)

*prior to argatroban hold for one step & prior to argatroban dose reduction for two step, SD=Standard Deviation

Table 3: Compliance with Transition Guidelines

Characteristic	Result
Number of bridge courses assessed for compliance (n=32): Fully assessed, n (%) Partially assessed, n (%)	 29 (90.6) 3 (9.4)
Bridge course compliance: Compliant, n (%) – PRIMARY ENDPOINT Noncompliant, n (%)	 8/32 (25) 24/32 (75)
Compliance Components Platelet count recovery before warfarin initiation, n (%) First dose of warfarin ≤ 5mg, n (%) INR prior to warfarin bridge, n (%) Overlap of ≥ 5 days, n (%) Co-therapy INR ≥ 4, n (%) Argatroban held ≥ 4 hrs before monotherapy INR, n (%) Two-step transition process attempted when appropriate, n (%) Argatroban restarted or return to prior dose if INR < 2, n (%) Argatroban dc’d when warfarin monotherapy INR > 2, n (%)	 25/32 (78.1) 28/32 (87.5) 32/32 (100) 21/29 (72.4) 26/29 (89.7) 27/29 (93.1) 9/15 (60) 3/5 (60) 29/29 (100)

Table 4: Transition Success*

Characteristic	Result
Number of transition courses assessed (n=32) Fully assessed, n (%) Partially assessed (monotherapy INR unavailable), n (%)	 29 (90.6) 3 (9.4)
Transition success	16/32 (50)
Success Components: Bridge course completed within 7 days, n (%) Absence of major or clinically relevant bleeding , n (%) Absence of thrombosis, n (%) Absence of subtherapeutic (INR <2) or supratherapeutic (INR >3.5) for next 2 morning INR checks, n (%) Absence of argatroban restarts within 5 days for low INR, n (%)	 22/31 (71) 26/32(81.3) 30/32 (93.8) 22/29 (75.9) 26/29 (89.7)

* Assessed in those with at least a 3-day bridge course and those in whom bridge was interrupted for a bleeding event

Additional Results

- **Thrombosis occurred in 2/32 (6.3%) both deep vein thrombosis**
- **Bleeding occurred in 6/32 (18.8%); major bleeding n=2, non-major n=4**
- **The mean ± SD platelet count for early warfarin initiation was 111.4 ± 30 x 10^9/L with a range of 70-139 x 10^9/L**
- **No overall relationship between components of compliance and overall success, all pairwise comparisons p > 0.1**
- **Transition success was numerically higher in those without a two-step process initiated versus those that underwent a two-step process, 83.3% versus 25%**

Discussion

- This project represents the largest post marketing evaluation of the argatroban to warfarin transition in acute HIT patients
- Our overall compliance rate of 25% and transition success rate of 50% support the complicated nature of this component of HIT management
- Although guidance of the argatroban to warfarin transition process is available from national guidelines and the argatroban prescribing information, the evidence supporting each component of the process is limited
- This transition process has the potential to increase length of stay
- Seven of the twenty-nine (24.1%) of patients had objective confirmation of increased length of stay due to the bridge course
- Our bleeding rate was higher than our thrombosis rate supporting the previously reported finding that bridging increases the risk of bleeding
- While most of our patients had HIT with thrombosis (69%), our thrombotic event rate post-bridge initiation was low
- Three areas within the argatroban to warfarin transition require further study to ensure clinicians have the most appropriate guidance for managing this process:
  - When can warfarin be safely initiated in HIT?
    - Early warfarin initiation was, at times, recommended by hematology
    - The rate of thrombosis with early warfarin initiation was 14.3% versus 4% in those without early initiation
    - No cases of thrombosis occurred when warfarin was initiated with a platelet count > 100 x 10^9/L
  - Is the co-therapy INR goal of 4 correct?
    - The need to obtain a co-therapy INR goal of 4 often led to an extended bridge duration ranging from 8-13 days
  - Is a two-step process for argatroban discontinuation necessary?
    - Employing a two-step process for discontinuing argatroban at the end of the bridge did not improve transition success for those with argatroban doses above 2 mcg/kg/minute

Conclusion

- Compliance with guidelines for transitioning HIT patients from argatroban to warfarin and transition success were low

Future Direction

- Discuss findings with key stakeholders in pharmacy and hematology to identify edits to guidelines for this transition

Disclosure: Authors of this presentation do not have any disclosures to report regarding financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter presented.