Standardizing the management of heparin-induced thrombocytopenia

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Heparin-induced thrombocytopenia (HIT) is a serious immunologically mediated condition associated with unfractionated heparin and, to a lesser extent, low-molecular-weight heparins (LMWHs). The frequency of HIT varies from 0.5% to 5%, depending on the patient population studied. It is caused by a complex formed between heparin and platelet factor 4, which yields platelet activation, endothelial cell injury, and increased thrombin generation. The clinical consequences of HIT are skin lesions in 10–20% of affected patients and arterial or venous thrombosis in up to 50% of such patients. There are two types of HIT: isolated HIT and HIT with thrombosis syndrome (HITTS). The American College of Chest Physicians (ACCP) recommends that the diagnosis of HIT should be considered if the platelet count decreases by 50% or if a thrombotic event occurs within 4–14 days of heparin initiation. The diagnosis should be confirmed by testing for HIT antibodies. Once HIT is suspected, all heparin agents must be discontinued and an alternative anticoagulant that does not cross-react should be initiated, regardless of the presence of acute thrombosis.

Purpose. An evidence-based heparin-induced thrombocytopenia (HIT) treatment protocol to standardize the management of confirmed or suspected HIT was developed.

Summary. In a retrospective review of 10 patients with known or suspected HIT over a two-year period, medical records were evaluated for baseline laboratory results, treatment selection, initial dosing and monitoring, discontinuation of heparin, and alternative therapies chosen. Six of 10 patients had antibody-confirmed HIT at admission. Nine patients received alternative anticoagulation therapy with one of two formulary direct thrombin inhibitor (DTI) agents, lepirudin and argatroban; 1 patient was given fondaparinux. Medical record analyses revealed deficiencies in both initial and transitional dose administration and renal function monitoring, order omissions, infusion-related medication errors, and treatments that were unsubstantiated, inappropriate, or lacking in regulatory approval. The new treatment protocol developed to assist physicians, pharmacists, and nurses with HIT management focused primarily on the two agents labeled for HIT, lepirudin and argatroban. The protocol established baseline levels for the selection of anticoagulation therapy as well as guidance in DTI selection, use, and monitoring. Guidelines for initial dosing and continuous infusion rates based on weight and detailed instructions in all aspects of therapy discontinuation (transition) were included. HIT treatments unsupported by data ensuring the efficacy and safety of therapies were excluded. Careful review of the relevant literature led to the inclusion of alternative anticoagulant treatments based on issues of safety, efficacy, cost, and convenience of dose forms.

Conclusion. A treatment protocol for HIT was developed and implemented in a tertiary care hospital in an effort to improve the management of patients suffering from this complication.

Index terms: Anticoagulants; Argatroban; Dosage; Errors, medication; Fondaparinux; Heparin; Lepirudin; Protocols; Rational therapy; Thrombocytopenia; Toxicity

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have been the mainstay of anticoagulation therapy in patients with HIT, and their use is supported by positive clinical outcomes in multiple prospective studies. Fondaparinux, a factor Xa inhibitor, has not been associated with HIT, and case reports have suggested that it may have a role in the management of acute HIT. Regardless of treatment with a DTI or factor Xa inhibitor, treatment of patients with HITs should be transitioned to warfarin to prevent the recurrence of thromboembolism. In addition, caution must be used with warfarin administration, as overaggressive dosing may increase the risk of thrombosis. Given the expense and risks associated with these DTIs and fondaparinux, it is important to discontinue their use once platelet counts have normalized or therapy has been appropriately transitioned to warfarin.4

**Problem**

DTI therapy is complex and costly and requires a multidisciplinary effort to minimize potential errors in its use, including prescribing, preparation, administration, and monitoring. Practice guidelines, medical and pharmacy literature, and product labeling provide detailed guidance on the optimal use of DTIs in treating HIT.1-8 However, the infrequent occurrence of HIT and the minimal use of DTIs leave most health care providers with a lack of sufficient experience in managing this disease. Our 508-bed tertiary care hospital has struggled with coordinating the complexities of this therapy. According to our pharmacists’ anecdotal observations, the health care team requested urgent consultations whenever HIT was suspected in a hospitalized patient. This motivated the pharmacy department to develop a HIT protocol to encompass the necessary components of patient evaluation; heparin discontinuation; alternative anticoagulant selection, dosing, and monitoring; and a seamless transition to oral anticoagulation or discontinuation of therapy. The goal of the protocol was to provide an effective tool in the form of an order set to guide each member of the health care team in the optimal and timely management of patients with known or suspected HIT.

**Analysis and resolution**

To verify these anecdotal observations, inpatient medical records for the two-year period before protocol development (from October 31, 2004, to October 31, 2006) were retrospectively reviewed with approval from the institutional review board. Ten patients were identified as having a HIT diagnosis or DTI use codes. Of these patients, six had antibody-confirmed HIT at admission; of the four unconfirmed cases, one patient was not tested and three had negative laboratory findings. Upon suspicion of HIT, nine patients received alternative anticoagulation therapy with one of the two formula- lary DTIs (lepirudin and argatroban), and one patient was given fondaparinux. Baseline laboratory test results, contraindications to therapy, and precautions were appropriately evaluated in the majority of cases. While initial dosing and monitoring were appropriate (with regard to patients’ renal and hepatic functions) in most cases, many deficiencies in DTI use were identified, including failure to administer a bolus dose at the initiation of DTI therapy, failure to measure the four-hour activated partial thromboplastin time (aPTT), and failure to measure patients’ renal function during lepirudin therapy. Only four patients received DTI dosage adjustments consistent with the manufacturer’s recommendations.

The transition to warfarin therapy was also an area where many deficiencies were noted. For example, the rate of DTI infusion was not reduced for most patients after the initiation of warfarin. Three patients received warfarin sodium dosages that exceeded the acceptable average maintenance dosage (>5 mg daily), one patient did not have a five-day overlap with the parenteral anticoagulant, and three were lacking two International Normalized Ratio (INR) results in the target range before discontinuation of the DTI. Specific heparin orders were discontinued in all patients with active orders; however, at DTI discontinuation, one patient received a heparin lock and another was prescribed enoxaparin. In addition, no explicit orders were written to avoid heparin or LMWHs.

Other problems included the failure to order the avoidance of intramuscular injections (6 patients) and the absence of nursing orders to monitor for bleeding or thrombosis (all 10 patients). One patient received fondaparinux for treatment of suspected HIT, and treatment in another was transitioned from lepirudin to fondaparinux despite the lack of evidence and FDA-approved labeling for this practice. The mean length of stay was 12.5 days after diagnosis of HIT.

These findings confirmed our anecdotal observations of suboptimal HIT management, despite the fact that the majority of cases were managed by consulting hematologists with the involvement of clinical staff pharmacists.

The protocol, as shown in the appendix, was developed using an evidence-based review of the literature.4-7,9,10 Diagnostic criteria for HIT were defined to distinguish it from heparin-associated thrombocytopenia, the mild drop in the platelet count that is not immunologically mediated. Our institution has the HIT–immunoglobulin G (IgG) antibody assay conducted at a reference laboratory, and results are usually available in two to four days. Due to the lengthy turnaround time for the HIT–IgG assay results, therapy is initiated in patients with suspected HIT rather than antibody-confirmed HIT. Critical orders that were frequently
omitted in past handwritten orders (i.e., nursing orders to monitor for bleeding and thrombosis and orders to discontinue all heparins and intramuscular injections) were included in the order set. Orders to establish baseline levels for selection of anticoagulation therapy were included in the protocol, as well as guidance in DTI selection, use, and monitoring in compliance with manufacturer recommendations.

In our institution, lepirudin is the first-line agent in the treatment of HIT; the protocol allows for argatroban only when the inclusion criteria for lepirudin are not met. Initial dosing and continuous infusion rates based on weight were provided in an easy-to-use table form. This is the most important section for preventing infusion-related medication errors that could easily occur with such complex regimens.

The final and most challenging section to develop was instructions for therapy discontinuation and transition. Both this section and the dosage adjustment section specified that orders were to be written separately from the protocol whenever a change in the orders occurred; this stipulation was designed to prevent medication errors and confusion due to the potential for multiple changes in infusion rate throughout the course of treatment.

Although the protocol includes features intended to assist physicians, pharmacists, and nurses with HIT management, education of the pharmacists on this new protocol required the greatest effort because other members of the health care team have traditionally relied on the pharmacy department to lead them through the complexities of treating HIT.

Discussion

The protocol was primarily developed around the two drugs with FDA-approved indications for HIT: lepirudin and argatroban. A review of the literature revealed three prospective studies of lepirudin and two prospective trials of argatroban. A combined analysis of the lepirudin studies found new thromboembolic complications in 7.4% of lepirudin-treated patients versus 25.0% of historical controls ($p < 0.0001$) and a composite endpoint (death, amputation, and new thromboembolic complications) in 20.3% of lepirudin-treated patients versus 43.3% of historical controls ($p < 0.0001$). The rate of major bleeding was significantly greater in lepirudin-treated patients (17.6%) than in historical controls (5.8%) ($p = 0.0015$). The mean maintenance dosage of lepirudin for these three studies ranged from 0.07 to 0.11 mg/kg/hr. A combined analysis of the argatroban trials indicated that argatroban significantly reduced the rate of new thrombosis (hazard ratio [HR], 0.29; 95% confidence interval [CI], 0.17–0.50) in the isolated HIT group; HR, 0.32; 95% CI, 0.18–0.55 in the HITTS group) compared with that of historical controls. In addition, the rate of the composite endpoint of death, amputation, and new thrombosis was reduced in argatroban-treated patients compared with that of historical controls (HR, 0.33; 95% CI, 0.20–0.54 in the isolated HIT group; HR, 0.39; 95% CI, 0.25–0.62 in the HITTS group). The rate of major bleeding was similar between groups.

One challenge we encountered in our protocol development was determining the extent to which our protocol should include alternative anticoagulation therapies that do not cause HIT but that lack both regulatory approval and sufficient evidence to support their use in HIT treatment. The DTI bivalirudin is labeled for use in patients undergoing percutaneous coronary intervention who have or are at risk for HIT, but bivalirudin was excluded from the protocol as it lacked regulatory approval and evidence of use in the treatment of acute HIT. Subcutaneous lepirudin and fondaparinux were considered for inclusion, as there is literature to support their use in the management of HIT. Subcutaneous lepirudin was excluded from our protocol because the 50-mg vial required unit dose repackaging into individual 25-mg syringes for twice-daily administration. In addition to this limitation, there were no definitive recommendations for monitoring this agent when given by this route. Several published case reports have described successful treatment with fondaparinux in patients with HITTS, isolated HIT, and a history of HIT. However, fondaparinux has not been studied in the clinical trial setting in patients with HIT and has not received labeling for this use. Warkentin and Greinacher stated that fondaparinux lacks in vitro cross-reactivity with HIT antibodies and may be appropriate for prevention of thrombosis in its low-dose regimen in the absence of HIT when there is a preference to avoid heparin—for example, in a thrombocytopenic patient judged unlikely to have HIT. The 2004 ACCP Conference on antithrombotic therapy declined to recommend fondaparinux in the treatment of acute HIT presumably due to the minimal data supporting its use in this disorder. Hassell, however, asserted that given the low rate of de novo antibody formation and the apparent lack of cross-reactivity with HIT antibodies, fondaparinux may represent a relatively safe alternative anticoagulant for use in patients with a history of HIT. Fondaparinux’s availability as a cost-effective and convenient dosage form designed for subcutaneous administration also adds to its usefulness for treatment of HIT. Therefore, fondaparinux was added to the protocol as an alternative anticoagulant for subacute or resolved HIT for patients whose treatment has not been transitioned to warfarin after DTI therapy or when alternative...
thromboprophylaxis or thromboembolic treatment is needed in a patient with a history of subacute or resolved HIT.

Another complexity of HIT management addressed by the protocol is the interpretation of the INR data. The INR should be corrected to ensure an accurate interpretation of the warfarin effect on the INR. INR correction is dependent on the dose of argatroban and the thromboplastin reagent used.

It is anticipated that the effort invested in this protocol will be rewarded with more appropriately, efficiently, and confidently managed HIT cases, resulting in improved patient outcomes. Further evaluation of this protocol to validate its effectiveness is planned.

Conclusion

A treatment protocol for HIT was developed and implemented in a tertiary care hospital in an effort to improve the management of patients suffering from this complication.

References


Appendix—Heparin-induced thrombocytopenia (HIT) order set

Criteria for the Evaluation of Suspected Acute HIT

≥50% drop in baseline platelet count (even if >150,000 platelets/μL)

Venous or arterial thrombotic event occurring within 4-14 days of heparin initiation

Note: A self-limiting, asymptomatic fall in platelet count (<100,000 platelets/μL) occurs in heparin-associated thrombocytopenia that is not immunologically mediated. No treatment is required. Heparin discontinuation is not required.

Initial Orders for Suspected or Confirmed Acute HIT

1. Discontinue all heparin or low-molecular-weight heparin administrations by any route.
2. Obtain baseline activated partial thromboplastin time (aPTT), serum creatinine (SCr), complete blood cell count (CBC), and comprehensive metabolic profile (CMP) laboratory test results immediately if not available.
3. Avoid intramuscular injections; contact the physician to change intramuscular injection orders.
4. Check for bleeding and signs of thrombosis once per shift; order testing of all suspicious stools for occult blood.
5. Obtain the HIT immunoglobulin G (HIT-IgG) antibody assay to confirm diagnosis.
Current Baseline Patient Data for Determining HIT Therapy

- Height (in) and weight (kg)
- SCr (mg/dL)
- Creatinine clearance (CL_c) (mL/min)
- Aspartate transaminase (AST) (units/L)
- Alanine transaminase (ALT) (units/L)
- aPTT (sec)

### Treatment Options for Acute HIT

**Lepirudin**

The following criteria must be met:
1. CL_c ≥ 15 mL/min and SCr ≤ 6 mg/dL.
2. Baseline aPTT ≤ 70 seconds before initiation of therapy.
3. Absence of hirudin hypersensitivity, major bleeding, and hemophilia.

**Note:** Antibody formation occurs in 44–74% of patients. This may result in delayed clearance and reduced dosage requirements. Serious anaphylactic reactions have occurred during initial or repeat administration. Vigilant monitoring is recommended, especially in patients receiving repeat courses of lepirudin.

### Treatment Options for Thrombosis in Patients with Subacute or Resolved HIT Not Fully Anti-coagulated with Warfarin

- **Lepirudin:** per above criteria
- **Argatroban:** per above criteria

**Fondaparinux**

The following criteria must be met:
1. CL_c ≥ 30 mL/min.
2. If transitioning from a DTI, initiate fondaparinux 4 hours after lepirudin or argatroban discontinuation.

### Lepirudin Dosage, Administration, and Monitoring

- **Normal renal function:** Bolus ______ mg (0.4 mg/kg) i.v. over 15–20 minutes followed by continuous infusion ______ mg/hr = ______ mL/hr (0.15 mg/kg/hr).
- **Decreased renal function:** Bolus ______ mg (0.2 mg/kg) i.v. over 15–20 minutes followed by continuous infusion ______ mg/hr = ______ mL/hr based on CL_c (0.075 mg/kg/hr if CL_c = 45–60 mL/min, 0.045 mg/kg/hr if CL_c = 30–44 mL/min, 0.0225 mg/kg/hr if CL_c = 15–29 mL/min).
- If >110 kg, administer bolus and infusion based on 110-kg weight.

### Bolus and Infusion Table

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Bolus (standard conc. = 5 mg/mL)</th>
<th>Continuous Infusion (standard conc. = 0.4 mg/mL)</th>
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<tbody>
<tr>
<td></td>
<td>Dose (mg)</td>
<td>Vol. (mL)</td>
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<tr>
<td>110</td>
<td>44</td>
<td>8.8</td>
</tr>
</tbody>
</table>

**>110 Administer 110-kg bolus | Administer 110-kg infusion based on creatinine clearance**

*Rounded to the nearest 5 kg.*
Monitoring target aPTT: 1.5–2.5 times baseline (baseline = 28 sec):

1. Obtain an aPTT value 4 hours after infusion is initiated. Repeat every 4 hours until in goal range twice consecutively.

2. Measure the aPTT value once daily unless an increased bleeding risk or prior lepirudin treatment indicates the need for more frequent monitoring.

3. Monitor renal function at least once daily. Indicate the frequency and type of panel needed (e.g., CMP).

4. Note the frequency of CBC monitoring.

Dosage adjustment:

| Supratherapeutic aPTT: For a confirmed aPTT of >70 seconds, stop infusion for 2 hours, restart the infusion at 50% of the initial infusion rate, and re-determine the aPTT 4 hours after the infusion is resumed. |
| Subtherapeutic aPTT: For a confirmed aPTT of <42 seconds, change the infusion rate in increments of 20% and re-determine the aPTT 4 hours after each dosage change. Caution: Do not exceed an infusion rate of 0.21 mg/kg/hr without checking for coagulation abnormalities. |

Subtherapeutic aPTT:

1. Initiate the appropriate warfarin sodium maintenance dose to a maximum of 5 mg orally daily (do not use loading doses). Consider initiating a lower daily dose (e.g., 2.5 mg) in patients with hepatic impairment, heart failure, or malnutrition as well as in those receiving interacting medications and in the elderly. Monitor the INR daily.

2. Aragatroban–warfarin cotherapy lasts 3–5 days, depending on the INR results:

If the argatroban dose is ≤2 μg/kg/min, take the INR daily without adjusting the dose.

If the argatroban dose is >2 μg/kg/min, decrease the infusion to 2 μg/kg/min, take the INR 6 hours later, and resume at the previous infusion level.

3. Daily INR interpretation with argatroban and warfarin cotherapy:

For INR values < 4, continue argatroban infusion.

For repeated INR values < 2, restart argatroban and warfarin cotherapy.

For repeated INR values ≥ 2, do not restart argatroban. Contact the prescriber to adjust the warfarin dose if above the therapeutic range.

The argatroban order may be discontinued after 2 consecutive days of INR values ≥ 2.

Daily Fondaparinux Dosing and Administration

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>2 μg/kg/min (normal hepatic function)</th>
<th>0.5 μg/kg/min (moderately decreased hepatic function)</th>
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<td>Rate (mL/hr)</td>
<td>Dose (μg/min)</td>
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* Rounded to the nearest 5 kg.

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