Development and Implementation of a Lepirudin Dosing Protocol for the Treatment of Heparin-Induced Thrombocytopenia and Associated Thromboembolic Disease in an Acute Care Setting

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Jennifer J. Hablewitz, R.Ph.

Pharm.D. Candidate August 2006
University of Florida
Working Professional Doctor of Pharmacy Program

Background:

Over 1 trillion units of heparin are used annually in the United states.[1] Heparin-induced thrombocytopenia (HIT) is a very serious adverse effect associated with the use of heparin. Two types of HIT are described. Type 1 HIT is a non-immune mediated process characterized by a transient drop in the platelet count early in the course of heparin therapy, usually between days 1 and 4.[2,3] Type 1 HIT does not require the discontinuation of heparin and it is generally reversible and asymptomatic.[2,3] Type 2 HIT is an immune-mediated process that can result in serious life and limb threatening consequences.[2,3,4] Type 2 HIT has been reported to affect up to 5% of patients exposed to heparin.[2,3,5] This paper will focus on Type 2 HIT and will refer to Type 2 HIT as HIT.

HIT is characterized by a drop in the platelet count >50% from baseline or <150,000µ/l, thromboses and thromboembolic complications (TECs).[4,5] HIT typically presents between days 5-14 after the start of heparin therapy, but may present earlier (within 12 hours) if the patient has been exposed to heparin in the previous 100 days.[2,4-6] Additionally, a delayed-onset HIT has been observed several days after the discontinuation of heparin.[2,4-6] HIT is most common with intravenous heparin, but can occur with any exposure to heparin including: subcutaneous heparin, heparin flushes, heparin-coated catheters and hemodialysis.[3,5] Low-molecular weight heparins have less commonly been associated with HIT and are generally contraindicated in patients with HIT.[2-7] The incidence of HIT while receiving low-molecular weight heparins is1% or less.[2,4,7]

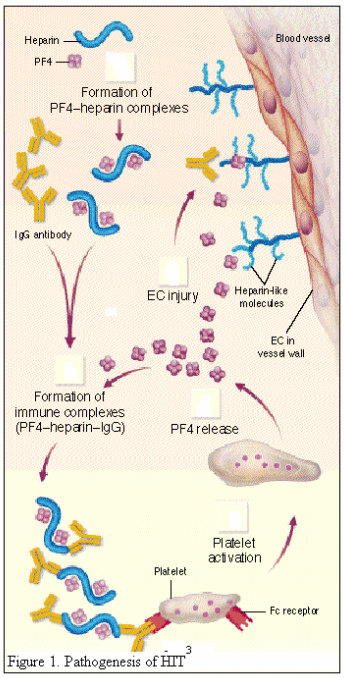

Figure 1. Pathogenesis of HIT[3]

The pathogenesis of HIT can be described in 3 stages (Figure 1). The first is the immune reaction, with the generation of HIT antibodies. Heparin binds to platelet factor 4 (PF4) released from platelets.[3,6,8] This complex is highly antigenic and stimulates the production of IgG antibodies.[3,6,8] Up to 18% of patients treated with heparin will develop the HIT antibodies, but most will not develop HIT.[9] Those patients that develop HIT proceed to stage 2 of the process. In this stage the heparin-PF4-IgG complex binds to the Fc receptors on the platelet surface resulting in platelet activation, the release of more PF4 and the production of prothrombotic microparticles.[2,3,6,8] Excess PF4 binds to heparin like glycosaminoglycans on the surface of the endothelial cell providing an additional target for antibody binding.[3,8] Antibody binding causes the release of tissue factor leading to the generation of thrombin.[2,3,6,8] Stage 3 is the extension of existing thrombosis or the development of new thrombosis.[3,6,8] TECs associated with HIT include: deep vein thrombosis, pulmonary embolism, limb artery occlusion, stroke, myocardial infarction and heparin-induced skin lesions.[2,3,6,8] More than 50% of patients who develop HIT will experience a

TEC if not effectively managed.[10,11] Once a patient experiences a TEC, mortality can be as high as 30% and 10-20% of patients will require limb amputation.[12] Thrombin plays a central role in the pathogenesis of HIT and is the target of current therapies for the treatment of HIT.

Two direct thrombin inhibitors, lepirudin and argatroban, are currently approved for the treatment of patients with HIT and associated TECs.[13] HIT and associated TECs is also known as HIT associated thrombosis syndrome (HITTS). Currently, lepirudin is the direct thrombin inhibitor on formulary at ThedaCare's two hospitals. There are no guidelines, clinical pathways or protocols in place to guide the use of lepirudin. The purpose of this paper is to review the literature evaluating the use of lepirudin in the treatment of HITTS, and to develop a protocol for the use of lepirudin in the treatment of HITTS at ThedaCare.

Evaluation of Practice Guidelines:

Guidelines for the recognition, treatment, and prevention of HIT, developed by the American College of Chest Physicians (ACCP) Task Force on Antithrombotic Therapy, were published in the September 2004 supplement issue of *Chest*. The authors discuss the fact that HIT is a prothrombotic condition associated with increased thrombin generation and emphasize treatments that target thrombin generation.[4] For the treatment of HIT the authors recommend "For patients with strongly suspected (or confirmed) HIT, whether or not complicated by thrombosis, we recommend use of an alternative, nonheparin anticoagulant, such as lepirudin (grade 1C+), argatroban (grade 1C), bivalrudin (grade 2C), or danaparoid (grade 1B), over further UFH or LMWH therapy, and over no further anticoagulation (with or without vena caval filter)."[4] The authors evaluated three lepirudin studies (a meta-analysis of HAT-1 and HAT-2, HAT 3 and the Drug Monitoring Program), in making their recommendations.[4]

Studies evaluating the use of lepirudin in the treatment of HIT:

A series of four studies and one meta-analysis evaluated the efficacy of lepirudin for anticoagulation in patients with confirmed HIT.

HAT-1:

The first of these studies was HAT-1.[14] This was a multicenter prospective cohort study which compared patients treated with lepirudin to historical controls. Four groups of patients were evaluated: HIT patients with thrombosis (n=51), HIT patients with thrombosis receiving thrombolysis (n=5), HIT patients without thrombosis (n=18), and during cardiopulmonay bypass surgery (n=8). Based on predefined exclusion criteria, 71 of the lepirudin patients were compared to the historical control group (n=120) for combined and individual incidences of death, limb amputations, new TECs and incidences of bleeding. A significant reduction of the combined end point (death, limb amputation, new TECs) was achieved with lepirudin treated patients (9.9% vs 23% at day 7 and 25.4% vs 52.1% at day 35, RRR 51%, p=0.014). Mortality in the lepirudin group was 8.6% vs 22.3% in the historical control group (RRR 61%, p=0.071). Incidences of

new TECs and limb amputations were less in the lepirudin group (18.4 %, 5.7%) compared to the historical control group (32.1%, 8.2%), but did not reach statistical significance. Cumulative incidences of bleeding events requiring transfusions were slightly higher in the lepirudin group (9.9%), but not significantly different (p=0.5889, log-rank test) from the historical control group (9.1%). No incidences of intracerebral or fatal hemorrhages were observed during the study.[11,14]

HAT-2:

The primary objective of HAT-2 was to confirm the clinical efficacy and safety reported in HAT-1.[15] HAT-2 again was a multicenter prospective cohort study comparing lepirudin treated patients to historical controls. Only two groups of patients were evaluated in HAT-2: HIT patients with thrombosis (n=69) and HIT patients without thrombosis (n=43). Based on the same predefined exclusion criteria for HAT-1, 95 of the lepirudin patients were compared to the same historical control group (n=120) for combined and individual incidences of death, limb amputations, new TECs and incidences of bleeding. The combined end point was less in the lepirudin group (30.9%, 95%CI, 21.0%-40.7%) than in the historical control group (52.1%, 95%CI, 40.4%-63.9%), but the difference did not reach statistical significance (p=0.12). Mortality in the lepirudin group was 10.5% (95%CI, 3.7%-17.3%) vs 22.3% (95%CI, 12.8%-31.9%) in the historical control group (p=0.12, log-rank test). Incidences of new TECS was 17.4% (95%CI, 9.6%-25.1%) vs 32.1% (95%CI, 21.1%-43.1%) in the historical control group (p=0.26). Incidences of limb amputations were slightly higher in the lepirudin group (10.0% [95%CI, 3.8%-16.1%] vs 8.2% [95%CI, 0.8%-15.5%]), but the difference was not statistically significant (p=0.43). In this study the lepirudin group had higher incidences of any documented bleeding event (44.6% [95%CI, 33.8%-55.4%] vs 27.2% [95%CI, 16.3%-38.0%] p=0.0001, log-rank test), but there was no statistically significant difference in bleeding events requiring transfusion (12.9% [95%CI, 6.1%-19.7%] vs 9.1% [95%CI, 3.7%-14.4%] p=0.23, log-rank test). No incidences of intracerebral or fatal hemorrhages were observed in HAT-2. An important finding in this study was that of patients that developed a new TEC, 45% developed the event before treatment was initiated.[11,15] This finding provides support that stopping heparin therapy alone is not an appropriate strategy for the management of a patient with HIT.

Meta-analysis of HAT-1 and HAT-2:

HAT-1 and HAT-2 included patients with HIT both with and without TECs at baseline. A meta-analysis of these two studies was done to evaluate the effects of lepirudin in the patients with TECs at baseline (n=113).[16] The same outcomes evaluated in HAT-1 and HAT-2 were evaluated in the meta-analysis and compared to the historical control group (n=75). A significant reduction in the combined end point was achieved in the lepirudin group compared to the historical control group (21.3% vs 47.8%, RRR 55%, p=0.0004, log-rank test). Incidences of new TECs were also significantly less in the lepirudin group (10.1% [95%CI, 4.4%-15.8%] vs 27.2% [95%CI, 16.6%-37.8%], RRR 63%, p=0.005, log-rank test). Incidences of death and limb amputation were slightly lower in the lepirudin group, but these differences did not reach statistical significance. (death-8.9% vs 17.6%, RRR 49%; limb amputation-6.5% vs 10.4%, RRR 38%). The time from diagnosis of HIT to the start of lepirudin therapy showed the highest risk for a clinical

event (mean 1.7 days). Incidences of bleeding and bleeding that required transfusion were both higher in the lepirudin group compared to the historical control group (bleeding 42.0% vs 23.6%, p=0.001; bleed requiring transfusion 18.8% vs 7.1%, p=0.02).[4,11,16] This study demonstrated the clinical benefits of treatment with lepirudin in patients with HITTS, but also highlights the risks of bleeding and the need for close monitoring of these patients.

HAT-3:

HAT-3 was a multicenter prospective study with multiple treatment arms (n=205).[17] The first arm of this study evaluated patients with HIT and TECs at baseline (n=98). Incidence of the combined endpoints of death, new TECs and amputations was 21.5%, RRR 55%. The incidences of death, new TECs and amputations were 14.3% RRR 19%, 6.1% RRR 78%, and 5.1% RRR 51% respectively. 20.4% of patients experienced major bleeding complications. 56.7% of all new TECs occurred prior to the start of treatment with lepirudin, again demonstrating the need to treat patients with HIT as soon as a clinical diagnosis is made.[4,17]

Drug Monitoring Program:

A large (n=1329) postmarketing observational study (Drug Monitoring Program) done in the setting of routine clinical practice, further examined the use of lepirudin in patients with HIT with TECs at baseline (n=496) and without TECs at baseline (n=612).[18] The remaining patients (n=221) were treated with lepirudin for other reasons (eg cardiopulmonary bypass). In evaluating the patients with TECs at baseline, the incidence of the combined endpoint was 21.9%. The incidence of death, amputation and new TECs was 10.9%, 5.8%, and 5.2% respectively. The individual endpoints are dramatically lower than the previously reported endpoints. In this study, the incidence of major bleeds was only 5.4%. There were no unexpected adverse events or risk factors during the course of this study.[4,18] Adverse effects in this study were substantially reduced compared with the previous clinical trials while maintaining efficacy.

Clinical Recommendations: HIT Working Group Consensus

The HIT Working Group is a consortium of 20 of the nation's leading experts in anticoagulation. The group convened in a series of meetings in which they sought to: identify gaps in the awareness of HIT, improve the diagnosis and treatment of HIT, and facilitate changes in the management of HIT that may result in optimal patient outcomes. In February 2005, the group released their recommendations. A brief summary of the recommendations include the following:[19,20]

-Implement educational programs designed to increase HIT awareness
-Encourage adoption of the ACCP guidelines on the management of HIT
-Creation and implementation of standardized HIT treatment protocols
-Multidisciplinary approach to HIT screening and treatment
-Place HIT at the forefront of medication safety concerns and encourage institutions to develop HIT protocols

HIT Working Group encourages pharmacist involvement:

Various members of the group have issued statements that support and encourage the involvement of pharmacists in carrying out the recommendations. Midori Kondo, Pharm.D. has stated "the pharmacist is key for this disease state." Pharmacists can work within their health-systems by participating in the development of a clinical protocol and increasing awareness of HIT among clinicians.[21] William Dager, Pharm.D. has commented that many clinicians are not familiar with the drugs used to treat HIT. He has suggested that the pharmacist can play a role in getting treatment started as quickly as possible.[22] Lawrence Rice, M.D has suggested many ways for the pharmacist to be involved in the management of HIT. He has stated that pharmacists can be an integral part of the monitoring of patients exposed to heparin and in the monitoring of patients treated with a direct thrombin inhibitor. He encourages the inclusion of pharmacists in the multidisciplinary approach to HIT management.[22] The HIT working group concluded that "healthcare providers must regard HIT as a life-threatening condition and approach care of HIT patients with appropriate urgency."[19,20,22]

Use of Lepirudin at ThedaCare:

As mentioned previously, lepirudin is the direct thrombin inhibitor on formulary at ThedaCare. Prior to December 2005 there were no guidelines, clinical pathways or protocols in place to guide the use of lepirudin. Frequently, physicians request pharmacists to dose and monitor patients initiated on lepirudin; however, in the absence of a standard guideline or protocol, it was difficult for pharmacists monitor and make dose adjustments without consulting with the physician.

In January 2005, the pharmacy practice resident at ThedaCare conducted a retrospective chart review of all patients that had received lepirudin for the treatment of HIT at ThedaCare from January 2003 through December 2004. The results and conclusions of the chart review were presented at the Great Lakes Pharmacy Resident Conference April 29, 2005.[23] The overall conclusion of this chart review was that a protocol for the use of lepirudin in the treatment of HIT is needed at ThedaCare.

Development of a Dosing Protocol:

With the availability of the 2004 Chest guidelines for the treatment of HIT, the results of our internal chart review and the recommendations of the HIT Working Group; it was clear that it was time to develop a protocol for the use of lepirudin in HIT at ThedaCare.

A multidisciplinary approach was used in developing the protocol. The first step was to discuss the development of a protocol with physicians that had been identified as ordering lepirudin in the past. The response was overwhelming. The physicians agreed that it would be beneficial to pursue the development of a dosing protocol. The hematology group of physicians agreed to be the primary contact group throughout the

development of the protocol. Input from pharmacists, nurses and lab technicians was also obtained. Again, there was a lot of support for a protocol and many suggestions were made on what type of information to include in the protocol.

ThedaCare currently has a heparin dosing protocol that has been very successful. This protocol includes: the written protocol, an order set for the initial dosing and dosage adjustments based on aPTT, and a flowsheet to document initial dosing, aPTT results and dose modifications. Based on the recommendations from pharmacists, nurses and physicians, this successful heparin protocol was used as a template for the lepirudin dosing protocol. It was felt that using this protocol as a template would ease the implementation of a new lepirudin protocol due to the widespread use and familiarity with the heparin protocol.

Throughout the development of the protocol, drafts were presented to the various multidisciplinary groups and changes were made based on their suggestions. In September 2005 the lepirudin protocol was presented to the Pharmacy and Therapeutics Committee for approval. Items presented that constitute the protocol included: a document detailing the guidelines for the use of lepirudin in HITTS, an order set for initial ordering and monitoring, and a flowsheet to document labs and dosages (Appendix A, B, C). The committee overwhelming approved the protocol and encouraged immediate implementation.

Implementation of the protocol:

Many steps were necessary to implement the protocol into clinical practice. The two most time consuming steps were education and development of an electronic version of the order set. Prior to implementation all the pharmacists were provided with education on the protocol. Written materials were distributed to the pharmacists and an educational in-service was offered as well. Any pharmacist that desired additional education was offered individualized education. An additional unexpected step, was the creation of an electronic version of the order set. The order set contains orders for nursing, lab and pharmacy. Because of the large number and complexity of the orders contained within the order set, an electronic version of the order set was developed within the electronic ordering system. By selecting the order set number, all the orders pertaining to the order set are displayed and can be ordered at one time. This eliminates the need to individually enter each of the orders into the pharmacy, nursing and lab electronic systems, reducing the potential for missed or inaccurately entered orders. The final step was communicating the availability of the protocol to the physicians. A review of the protocol was included in the quarterly Pharmacy and Therapeutics Committee newsletter, the protocol was posted to the guidelines and protocols section of the ThedaCare intranet, and face to face information was provided to physicians that routinely use lepirudin.

Experience with the protocol:

The protocol was approved as both a pharmacy driven protocol and a physician driven protocol. As a pharmacy driven protocol, a physician can write an order for "pharmacy to dose lepirudin per protocol" and the clinical pharmacist is responsible to initiate the lepirudin and make all of the necessary dosage adjustments based on the protocol. As a physician driven protocol, the physician can initiate the protocol without the involvement of pharmacy. In this scenario, the clinical pharmacist will still closely monitor the patient and made recommendations to the ordering physician if his/her orders deviate from the protocol. Since the availability of the protocol, two patients have been initiated on lepirudin. In both of these cases, the physicians consulted pharmacy to dose the lepirudin. In both cases, the protocol worked well and overall satisfaction with the use of the protocol was very high. One area that could be improved upon is the use of the flowsheet. Currently two copies of the flowsheet are being maintained. One copy is kept in the patient's chart and another is maintained within the pharmacist's monitoring file. Work is in progress with the information technology department to create an electronic version of the flowsheet. Creation of an electronic version will eliminate the need for duplicate work and reduce the risk of errors while maintaining two copies of the same information. The information technology department is also working on having the lab results and lepirudin dosages automatically populate into the electronic flowsheet. The availability of an electronic form will allow viewing of this information from any computer that has the ability to access the patient's electronic medical record.

Conclusion:

It is well documented that HIT is a serious life and limb threatening complication of the use of heparin. Studies that have evaluated the use of lepirudin in the treatment of patients with HITTS have demonstrated significant improvements in outcomes. The HIT Working Group has issued a strong statement that health systems need to incorporate the ACCP guidelines for HIT into their practice settings. The overall goal of this project was to develop and implement a lepirudin protocol for the treatment of HITTS within the ThedaCare system. The protocol was implemented in December 2005 and has been widely accepted throughout ThedaCare. Implementation of the lepirudin protocol is predicted to improve the pharmaceutical care of patients with HITTS. ThedaCare will attempt to quantify the impact of the protocol by conducting a chart review in six months.

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