Patients with a diagnosis of acute deep venous thrombosis have traditionally been hospitalized and treated with unfractionated heparin followed by oral anticoagulation therapy. Several clinical trials have shown that low-molecular-weight heparin is at least as safe and effective as unfractionated heparin in the treatment of uncomplicated deep venous thrombosis. The use of low-molecular-weight heparin in an outpatient program for the management of deep venous thrombosis provides a treatment alternative to hospitalization in selected patients. Use of low-molecular-weight heparin on an outpatient basis requires coordination of care, laboratory monitoring, and patient education and participation in treatment. Overlapping the initiation of warfarin permits long-term anticoagulation. Advantages include a decreased incidence of heparin-induced thrombocytopenia and fewer episodes of bleeding complications. Future clinical trials evaluating the safety and efficacy of low-molecular-weight heparin in the treatment of complicated deep venous thrombosis will further define appropriate indications for use and strategies for outpatient management.

Deep venous thrombosis (DVT) is associated with more than 600,000 hospitalizations annually in the United States and results in more than 200,000 deaths caused by pulmonary embolism. Patients with a diagnosis of acute DVT have traditionally been hospitalized and treated with a continuous infusion of unfractionated heparin for five to 10 days, followed by oral anticoagulation therapy for at least three months. Hospitalization has traditionally been considered necessary because of concerns about fatal pulmonary embolism (and the need for careful laboratory monitoring), but this risk is now known to be low during the initial treatment of DVT. Because of the wide variability in anticoagulant response among patients treated with unfractionated heparin, frequent monitoring of the activated partial thromboplastin time (aPTT) and dosage adjustments are required to keep anticoagulation in the therapeutic range. In most patients who have no major risk factors for bleeding or subsequent pulmonary embolism, such as protein C or S deficiency, history of previous pulmonary embolism or more proximal DVT, hospitalization is necessary only for monitoring aPTT and adjusting unfractionated heparin therapy.

Several clinical trials have shown that low-molecular-weight heparins are at least as safe and effective as unfractionated heparin in the treatment of DVT. These agents have a longer half-life and a more predictable anticoagulant response than unfractionated heparin, which allows for subcutaneous administration without laboratory monitoring. The use of low-molecular-weight heparins in the treatment of DVT provides an opportunity to realize significant cost savings by preventing or shortening hospitalization and by increasing patient comfort and satisfaction with health care. Shifting the management of DVT to the ambulatory setting presents several clinical and logistical challenges for clinicians, administrators and patients. The success of an out-patient program for the management of DVT depends on familiarity with currently available low-molecular-weight heparins, patient selection, protocol development and outcome evaluation.

Low-Molecular-Weight Heparins
Low-molecular-weight heparins are derived from depolymerization of standard heparin, which yields fragments approximately one third the size of the parent compound. These lower-molecular-weight fractions have several properties that differentiate them from unfractionated heparin. Low-molecular-weight heparins exert their anticoagulant effect by inhibiting factor Xa and augmenting tissue-factor-pathway inhibitor but minimally affect thrombin, or factor IIa (Figure 1a and 1b). Thus, the aPTT, a measure of antithrombin (anti-factor IIa) activity, is not used to measure the activity of low-molecular-weight heparins, which requires instead a specific anti-Xa assay.

**FIGURE 1A.**
Effect of low-molecular-weight heparin (LMWH) and unfractionated heparin on factor IIa and factor Xa. Both types of heparin inactivate factor Xa by interacting with antithrombin. Longer chain, unfractionated heparin (UFH) is able to inactivate factor IIa through formation of a tertiary complex, unlike LMWH. Compared with LMWH, UFH binds more to plasma proteins, endothelium and macrophages, resulting in reduced bioavailability and greater patient variability to a given dose. UFH inactivates factors IIa and Xa and affects the aPTT, a measure of anti-factor IIa activity. (aPTT = activated partial thromboplastin time)
Low-molecular-weight heparin inhibits factor Xa and minimally affects factor IIa; thus activated partial thromboplastin time is not used to measure its anticoagulant activity.

In addition to having lower antithrombin activity than unfractionated heparin, low-molecular-weight heparins bind less to plasma proteins, endothelium and macrophages, permitting greater bioavailability and little inter-patient and intra-patient variability in response to a given dosage. Clinical trials have confirmed that effective antithrombotic activity can be consistently achieved by calculating dosages based on body weight without the need for laboratory monitoring.

Since these agents are eliminated primarily through the kidneys, accumulation of anti-factor Xa activity may occur in patients with chronic renal insufficiency. Plasma anti-factor Xa concentrations should be monitored in patients with renal dysfunction and possibly in those weighing less than 50 kg (110 lb) or more than 80 kg (176 lb). Low-molecular-weight heparins also appear to be associated with less bleeding and a decreased frequency of heparin-induced thrombocytopenia, as a result of their lower affinity for platelets and von Willebrand factor. Danaparoid (Orgaran) and
lepirudin (Refludan) are indicated in the treatment of heparin-induced thrombocytopenia type II. Lepirudin is a recombinant form of hirudin, an anticoagulant derived from the saliva of leeches. Danaparoid is a low-molecular-weight heparin composed of a mixture of heparan, dermatan and chondroitin sulfates.

Low-molecular-weight heparins currently available in the United States include enoxaparin (Lovenox), dalteparin (Fragmin) and ardeparin (Normiflo), while nadroparin (Fraxiparine), tinzaparin (Logiparin, Innohep) and reviparin (Clivarine) are marketed elsewhere (Table 1). Enoxaparin was recently labeled by the U.S. Food and Drug Administration for outpatient treatment of DVT and may also be used in the inpatient setting to manage DVT with or without pulmonary embolism. Each of these agents is prepared with a different method of depolymerization, resulting in distinct molecular weights (4,000 to 5,500 Da) and relative effects on factor Xa and thrombin. For this reason, low-molecular-weight heparins are unique and not necessarily therapeutically interchangeable, although their pharmacologic and clinical characteristics are similar.

### TABLE 1
**Comparison of Low-Molecular-Weight Heparins**

<table>
<thead>
<tr>
<th>AGENT</th>
<th>CLINICAL TRIAL TREATMENT DOSES (ANTI-XA UNITS)</th>
<th>AVERAGE MOLECULAR WEIGHT (DA)</th>
<th>INTRAVENOUS HALF-LIFE (MINUTES)</th>
<th>COST*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ardeparin (Normiflo)†</td>
<td>Not evaluated</td>
<td>6,000</td>
<td>200</td>
<td>$154.50‡</td>
</tr>
<tr>
<td>Dalteparin (Fragmin)†</td>
<td>100 U per kg twice daily</td>
<td>5,000</td>
<td>119 to 139</td>
<td>63.00§</td>
</tr>
<tr>
<td>Enoxaparin (Lovenox)†</td>
<td>100 U per kg twice daily</td>
<td>4,500</td>
<td>129 to 180</td>
<td>78.50</td>
</tr>
<tr>
<td>Nadroparin (Fraxiparine)</td>
<td>225 U per kg twice daily</td>
<td>4,500</td>
<td>132 to 162</td>
<td>NA</td>
</tr>
<tr>
<td>Reviparin (Clivarine)</td>
<td>100 U per kg twice daily</td>
<td>4,300</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Tinzaparin (Logiparin, Innohep)</td>
<td>175 U per kg once daily</td>
<td>4,900</td>
<td>111</td>
<td>NA</td>
</tr>
<tr>
<td>AGENT</td>
<td>CLINICAL TRIAL TREATMENT DOSES (ANTI-XA UNITS)</td>
<td>AVERAGE MOLECULAR WEIGHT (DA)</td>
<td>INTRAVENOUS HALF-LIFE (MINUTES)</td>
<td>COST*</td>
</tr>
<tr>
<td>----------------</td>
<td>-----------------------------------------------</td>
<td>-------------------------------</td>
<td>-------------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Danaparoid</td>
<td></td>
<td>750 U twice daily</td>
<td>5,500</td>
<td>24 hours</td>
</tr>
</tbody>
</table>

Danaparoid (Orgaran)

Anti-Xa = plasma anti-factor Xa; Da = dalton (atomic mass unit); NA = not available.

*—Unless otherwise noted, estimated cost to the pharmacist for one day's therapy, rounded to the nearest half dollar, based on average wholesale prices in Red book. Montvale, N.J.: Medical Economics Data, 1998. Cost to the patient will be higher, depending on prescription filling fee.

†—Available in the United States.

‡—Price given is for 10 vials of medication (5,000 units per 0.5 mL). No dosing recommendation is given.

§—Price given is for treatment of a 70-kg (154-lb) adult.

∥—Indicated for heparin-induced thrombocytopenia only.

Information from references 9 and 10.

Several meta-analyses have indicated that low-molecular-weight heparins are superior to unfractionated heparin in the treatment of patients with established DVT. One analysis did not indicate a significant difference in symptomatic recurrence rates or adverse events but did note trends favoring low-molecular-weight heparins. The safety and effectiveness of these agents were significantly better than that of unfractionated heparin in two other analyses. Collectively, the results reveal a statistically significant reduction in thrombus size, recurrent venous thromboembolism, major bleeding events and pooled long-term mortality rate. Although the lower mortality rates observed in these trials were mostly attributable to a subgroup of patients with cancer, the data may indicate greater efficacy of low-molecular-weight heparins in this high-risk population.

Two recent studies of patients with DVT have also been conducted to compare the effect of low-molecular-weight heparins given on an outpatient basis subcutaneously twice daily with that of unfractionated heparin given by continuous intravenous infusion in the hospital. No significant difference was found in rates of recurrent venous thromboembolism, hemorrhagic complications, development of thrombocytopenia or mortality. Low-molecular-weight heparins were as safe and effective as unfractionated heparin, and most patients were managed at home immediately after diagnosis or a brief hospitalization.
Regional Anesthesia in the Anticoagulated Patient: Defining the Risks (The Second ASRA Consensus Conference on Neuraxial Anesthesia and Anticoagulation)

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Neuraxial anesthesia and analgesia provide several advantages over systemic opioids, including superior analgesia, reduced blood loss and need for transfusion, decreased incidence of graft occlusion, and improved joint mobility following major knee surgery.1-4 New challenges in the management of patients undergoing neuraxial block have arisen over the last 2 decades, as medical standards for the prevention of perioperative venous thromboembolism were established.5,6 Concern for patient safety in the presence of potent antithrombotic drugs has resulted in avoidance of regional anesthesia. Indeed, perioperative anesthesia and analgesia are often determined by the antithrombotic agent.7 Conversely, although the anesthesia community is well aware of the potential for spinal bleeding, other specialties have only recently become cognizant of the risk, as documented by case reports published in the cardiology and neurology literature.8,9

In response to these patient safety issues, the American Society of Regional Anesthesia and Pain Medicine (ASRA) convened its Second Consensus Conference on Neuraxial Anesthesia and Anticoagulation. Portions of the material presented here were published as the proceedings of the 1998 ASRA Consensus Conference.10-14 The information has been updated to incorporate additional data available since the time of its publication. It is important to note that although the consensus statements are based on a thorough evaluation of the available information, in some cases data are sparse. Numerous studies have documented the safety of neuraxial anesthesia and analgesia in the anticoagulated patient. Unfortunately, with a complication as rare as spinal hematoma, no clinical study to date has sufficient power to definitively determine patient management. Consequently, the pharmacology of hemostasis-altering drugs and case reports of spinal hematoma are also essential to regional anesthetic management. Variance from recommendations contained in this document may be acceptable based on the judgment of the responsible anesthesiologist. The consensus statements are designed to encourage safe and quality patient care, but cannot guarantee a specific outcome. They are also subject to timely revision as justified by evolution of information and practice. Finally, the current information focuses on neuraxial blocks and anticoagulants; the risk following plexus and peripheral techniques remains undefined. Although several case reports of vascular injury with (or without) resultant nerve dysfunction have been described,15,16 additional experience is needed to allow statements for non-neuraxial blocks. The current literature involving hemorrhagic complications of plexus and peripheral block is included for completeness.
tion, or a preexisting hypercoagulable condition. In anticipation of surgery, warfarin is discontinued and the prothrombin time allowed to normalize. During this time, the patient would be at risk for thromboembolic events, and historically would be hospitalized and heparinized systemically. Outpatient LMWH is a suitable alternative. The doses of LMWH are those associated with DVT treatment, not prophylaxis, and are much higher (Table 1). Needle placement should occur a minimum of 24 hours following this level of LMWH anticoagulation. It is also important to determine when the first postoperative dose is anticipated, because these patients are often aggressively anticoagulated postoperatively. In these cases, a spinal or a general anesthetic may be the safest alternatives.

Efficacy of Management Guidelines in Reducing the Risk of Spinal Hematoma

Perioperative management of patients receiving LMWH requires coordination and communication. Time intervals between neuraxial needle placement and administration of LMWH must be maintained. However, hospital staffs often administer LMWH at a set time (usually 7 to 8 AM and 7 to 8 PM), unless otherwise specified. It is also important to note that when protocols for dosing of LMWH and catheter management exist, they may not be closely followed. McEvoy et al. reported a 52% noncompliance rate in the administration of LMWH in association with epidural analgesia. Clinicians are urged to develop protocols that “fit” within the normal practice standards at their institutions rather than deviate from the routine.

Anesthetic Management of the Patient Receiving LMWH

Anesthesiologists in North America can draw on the extensive European experience to develop practice guidelines for the management of patients undergoing spinal and epidural blocks while receiving perioperative LMWH. All consensus statements contained herein respect the labeled dosing regimens of LMWH as established by the FDA. Although it is impossible to devise recommendations that will completely eliminate the risk of spinal hematoma, previous consensus recommendations have appeared to improve outcome. Concern remains for higher dose applications, where sustained therapeutic levels of anticoagulation are present.

Monitoring of the anti-Xa level is not recommended. The anti-Xa level is not predictive of the risk of bleeding and is, therefore, not helpful in the management of patients undergoing neuraxial blocks.

Antiplatelet or oral anticoagulant medications administered in combination with LMWH may increase the risk of spinal hematoma. Concomitant administration of medications affecting hemostasis, such as antiplatelet drugs, standard heparin, or dextran, represents an additional risk of hemorrhagic complications perioperatively, including spinal hematoma. Education of the entire patient care team is necessary to avoid potentiation of the anticoagulant effects.

The presence of blood during needle and catheter placement does not necessitate postponement of surgery. However, initiation of LMWH therapy in this setting should be delayed for 24 hours postoperatively. Traumatic needle or catheter placement may signify an increased risk of spinal hematoma, and it is recommended that this consideration be discussed with the surgeon.

Preoperative LMWH

Patients on preoperative LMWH thromboprophylaxis can be assumed to have altered coagulation. In these patients, needle placement should occur at least 10 to 12 hours after the LMWH dose.

Patients receiving higher (treatment) doses of LMWH, such as enoxaparin 1 mg/kg every 12 hours, enoxaparin 1.5 mg/kg daily, dalteparin 120 U/kg every 12 hours, dalteparin 200 U/kg daily, or tinzaparin 175 U/kg daily will require delays of at least 24 hours to assure normal hemostasis at the time of needle insertion.

Neuraxial techniques should be avoided in patients administered a dose of LMWH 2 hours preoperatively (general surgery patients), because needle placement would occur during peak anticoagulant activity.

Postoperative LMWH

Patients with postoperative initiation of LMWH thromboprophylaxis may safely undergo single-injection and continuous catheter techniques. Management is based on total daily dose, timing of the first postoperative dose, and dosing schedule.

Twice Daily Dosing. This dosage regimen may be associated with an increased risk of spinal hematoma. The first dose of LMWH should be administered no earlier than 24 hours postoperatively, regardless of anesthetic technique, and only in the presence of adequate (surgical) hemostasis. Indwelling catheters should be removed prior to initiation of LMWH thromboprophylaxis. If a continuous technique is selected, the epidural catheter may be left indwelling overnight and removed the following day, with the first dose of LMWH administered 2 hours after catheter removal.
**Single Daily Dosing.** This dosing regimen approximates the European application. The first postoperative LMWH dose should be administered 6 to 8 hours postoperatively. The second postoperative dose should occur no sooner than 24 hours after the first dose. Indwelling neuraxial catheters may be safely maintained. However, the catheter should be removed a minimum of 10 to 12 hours after the last dose of LMWH. Subsequent LMWH dosing should occur a minimum of 2 hours after catheter removal.

**Oral Anticoagulants (Warfarin)**

**Warfarin Pharmacology**

Oral anticoagulants, including warfarin, exert their anticoagulant effect indirectly by interfering with the synthesis of the vitamin K-dependent clotting factors, factor II (thrombin), VII, IX, and X. The effects of warfarin are not apparent until a significant amount of biologically inactive factors are synthesized and is dependent on factor half-life: factor VII, 6 to 8 hours; factor IX, 24 hours; factor X, 25 to 60 hours; and factor II, 50 to 80 hours.

An understanding of the correlation between the various vitamin K-dependent factor levels and the INR is critical to regional anesthetic management. Clinical experience with patients who congenitally are deficient in factors II, IX, or X suggests that a factor activity level of 40% for each factor is adequate for normal or near-normal hemostasis. Bleeding may occur if the level of any clotting factor is decreased to 20% to 40% of baseline. The PT and INR are most sensitive to the activities of factors VII and X and are relatively insensitive to factor II. Because factor VII has a relatively short half-life, prolongation of the PT and INR may occur in 24 to 36 hours. Prolongation of the INR (INR > 1.2) occurs when factor VII activity is reduced to approximately 55% of baseline, while an INR = 1.5 is associated with a factor VII activity of 40%. Thus, an INR < 1.5 should be associated with normal hemostasis.

The same principles apply during recovery of normal hemostasis upon discontinuation of warfarin therapy. Factor VII activity will rapidly increase, as demonstrated by a decrease in the INR. However, factor II and X activities recover much more slowly; hemostasis may not be adequate even though the INR is 1.4 or less. Adequate levels of all vitamin K-dependent factors are typically present when the INR is in the normal range. In emergent situations, the effects of warfarin may be reversed by injection of vitamin K and/or transfusion of fresh frozen plasma.

**Factors Affecting Warfarin Response**

The measured response to anticoagulant therapy at the initiation of treatment varies significantly. Some of the variability may be attributed to drug interactions, but in addition there are patient variables, such as age, female gender, and preexisting medical conditions (lower patient weight, liver, cardiac, and renal disease) that are associated with an enhanced response to warfarin. Oriental patients require lower doses than Caucasian patients during chronic therapy. In addition, there are many drug interactions described with warfarin therapy that potentiate the anticoagulant effect, including concomitant administration of antiplatelet medications, heparin, and LMWH.

Warfarin is a drug with a narrow therapeutic range. Attention to the individual patient’s response to warfarin therapy and maintenance of a consistent level of anticoagulation is paramount. Most medical laboratories have a method of contacting the caregiver in the event of an excessively prolonged PT/INR. However, further precautions may be warranted. Inclusion of pharmacy personnel may be one technique to add consistency in warfarin management. Because all warfarin orders are filled by the pharmacy (and entered into a central computer), linking the pharmacy and laboratory results’ computers will allow identification of patients with (1) a significant increase in the INR in a predefined time, (2) a subtherapeutic INR, and (3) warfarin therapy without INR assessment. The pharmacy then notifies the primary service and/or pain service so that appropriate action may be taken. To maintain the desired anticoagulant effect, the patient is instructed in a “warfarin” diet that contains foods with a consistent (low) level of vitamin K. These procedures have been successfully implemented at the Mayo Clinic.

**Neuraxial Techniques in the Chronically Anticoagulated Patient**

Although no studies have directly examined the risk of procedure-related bleeding and the INR in patients recently discontinued from warfarin, careful consideration should be given before performing neuraxial blocks in these patients. Labeling of warfarin in the United States specifically lists spinal puncture and lumbar block anesthesia as contraindicated during warfarin therapy that is not interrupted prior to surgery. Wille-Jorgensen et al. reported a case of difficult epidural placement in a patient fully anticoagulated with phenprocoumon. The anticoagulant therapy was unknown to the anesthesiologist. There was no bleeding observed during catheter placement, although placement was technically difficult. Satisfac-
PT/INR reflect predominantly factor VII levels, and despite acceptable factor VII levels, factors II and X levels may not be adequate for normal hemostasis. Adequate levels of II, VII, IX, and X may not be present until the PT/INT is within normal limits.

The concurrent use of medications that affect other components of the clotting mechanisms may increase the risk of bleeding complications for patients receiving oral anticoagulants, and do so without influencing the PT/INR. These medications include aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), ticlopidine and clopidogrel, unfractionated heparin, and LMWH.

For patients receiving an initial dose of warfarin prior to surgery, the PT/INR should be checked prior to neuraxial block if the first dose was given more than 24 hours earlier or a second dose of oral anticoagulant has been administered.

Patients receiving low-dose warfarin therapy during epidural analgesia should have their PT/INR monitored on a daily basis and checked before catheter removal, if initial doses of warfarin are administered more than 36 hours preoperatively. Initial studies evaluating the safety of epidural analgesia in association with oral anticoagulation utilized mean daily doses of approximately 5 mg warfarin. Higher dose warfarin may require more intensive monitoring of the coagulation status.

As thromboprophylaxis with warfarin is initiated, neuraxial catheters should be removed when the INR is <1.5. This value was derived from studies correlating hemostasis with clotting factor activity levels greater than 40%.

Neurologic testing of sensory and motor function should be performed routinely during epidural analgesia for patients on warfarin therapy. The type of analgesic solution should be tailored to minimize the degree of sensory and motor block. These checks should be continued after catheter removal for at least 24 hours, and longer if the INR was greater than 1.5 at the time of catheter removal.

An INR > 3 should prompt the physician to withhold or reduce the warfarin dose in patients with indwelling neuraxial catheters. We can make no definitive recommendation for removal of neuraxial catheters in patients with therapeutic levels of anticoagulation during neuraxial catheter infusion.

Reduced doses of warfarin should be given to patients who are likely to have an enhanced response to the drug.

**Antiplatelet Medications**

**Pharmacology of “Antiplatelet” Medications**

Antiplatelet agents include NSAIDs, thienopyridine derivatives (ticlopidine and clopidogrel), and platelet GP IIb/IIIa receptor antagonists (abciximab, eptifibatide, and tirofiban). It is important to note the pharmacologic differences among the drugs with antiplatelet effects.

Cyclooxygenase (COX) exists in 2 forms. COX-1 regulates constitutive mechanisms, while COX-2 mediates pain and inflammation. NSAIDs inhibit platelet COX and prevent the synthesis of thromboxane A2. Platelets from patients who have been taking these medications have normal platelet adhesion to subendothelium and normal primary hemostatic plug formation. Depending on the dose administered, aspirin (and other NSAIDs) may produce opposing effects on the hemostatic mechanism. For example, platelet COX is inhibited by low-dose aspirin (60 to 325 mg/d) while larger doses (1.5 to 2 g/d) will also inhibit the production of prostacyclin (a potent vasodilator and platelet aggregation inhibitor) by vascular endothelial cells. It has been suggested that the Ivy bleeding time is the most reliable predictor of abnormal bleeding in patients receiving antiplatelet drugs. However, there is no evidence to suggest that a bleeding time can predict hemostatic compromise. Platelet function is affected for the life of the platelet following aspirin ingestion; other nonsteroidal analgesics (naproxen, piroxicam, ibuprofen) produce a short-term defect, which normalizes within 3 days.

Celecoxib (Celebrex, Pfizer, New York, NY) and Rofecoxib (Vioxx, Merck and Co. Inc., Whitehouse Station, NY) are anti-inflammatory agents that primarily inhibit COX-2, an inducible enzyme which is not expressed in platelets, and thus does not cause platelet dysfunction. After single and multidosing, there have not been findings of significant disruption of platelet aggregation, nor is there a history of undesirable bleeding events. The concomitant use of COX-2 inhibitors and warfarin may increase the risk of hemorrhagic complications by increasing the PT.

The antiplatelet effect of the thienopyridine derivatives, ticlopidine and clopidogrel, results from inhibition of adenosine diphosphate (ADP)-induced platelet aggregation. These antiplatelet agents, used in the prevention of cerebrovascular thromboembolic events, affect both primary and secondary platelet aggregation. Ticlopidine (Ticlid, Roche Laboratories, Nutley, NJ) and clopidogrel (Plavix, Bristol-Myers Squibb Co., New York, NY) also interfere with platelet-fibrinogen binding and subsequent platelet-platelet interactions. Thienopyridine derivatives demonstrate both time- and dose-dependent effects; steady state is achieved within 7 days for clopidogrel and 14 to 21 days for ticlopidine. Although often administered in combination with antiplatelet medications, we can make no recommendation for either.
sites, and spinal hematoma. For example, in the series of 40 spinal hematomas associated with LMWH reported in 1998, 10 patients received concomitant antiplatelet medications. Likewise, in a case report of spinal hematoma following epidural steroid injection, Benzon et al. noted the patient had received multiple antiplatelet medications, including clopidogrel and aspirin.

Anesthetic Management of the Patient Receiving Antiplatelet Medications

Antiplatelet medications, including NSAIDs, thienopyridine derivatives (ticlopidine and clopidogrel), and platelet GP IIb/IIIa antagonists (abciximab, eptifibatide, tirofiban) exert diverse effects on platelet function. The pharmacologic differences make it impossible to extrapolate between the groups of drugs regarding the practice of neuraxial techniques. There is no wholly accepted test, including the bleeding time, which will guide antiplatelet therapy. Careful preoperative assessment of the patient to identify alterations of health that might contribute to bleeding is crucial. These conditions include a history of easy bruising/excessive bleeding, female gender, and increased age. NSAIDs appear to represent no added significant risk for the development of spinal hematoma in patients having epidural or spinal anesthesia. The use of NSAIDs alone does not create a level of risk that will interfere with the performance of neuraxial blocks.

At this time, there do not seem to be specific concerns as to the timing of single-shot or catheter techniques in relationship to the dosing of NSAIDs, postoperative monitoring, or the timing of neuraxial catheter removal.

The actual risk of spinal hematoma with ticlopidine and clopidogrel and the GP IIb/IIIa antagonists is unknown. Consensus management is based on labeling precautions and the surgical, interventional cardiology/radiology experience.

Based on labeling and surgical reviews, the suggested time interval between discontinuation of thienopyridine therapy and neuraxial block is 14 days for ticlopidine and 7 days for clopidogrel. Platelet GP IIb/IIIa inhibitors exert a profound effect on platelet aggregation. Following administration, the time to normal platelet aggregation is 24 to 48 hours for abciximab and 4 to 8 hours for eptifibatide and tirofiban. Neuraxial techniques should be avoided until platelet function has recovered. Although GP IIb/IIIa antagonists are contraindicated within 4 weeks of surgery, should one be administered in the postoperative period (following a neuraxial technique), the patient should be carefully monitored neurologically.

The concurrent use of other medications affecting clotting mechanisms, such as oral anticoagulants, unfractionated heparin, and LMWH, may increase the risk of bleeding complications. COX-2 inhibitors have minimal effect on platelet function and should be considered in patients who require anti-inflammatory therapy in the presence of anticoagulation.

Effects of Herbal Therapies on Coagulation

There is a widespread use of herbal medications in surgical patients. Most patients do not volunteer information regarding herbal medication use; obtaining such a history may be difficult. Morbidity and mortality associated with herbal use may be more likely in the perioperative period because of the polypharmacy and physiological alterations that occur. Such complications include bleeding from garlic, ginkgo, and ginseng, and potential interaction between ginseng-warfarin (Table 5). Be-
Neuraxial Anesthesia and Anticoagulation

(Based on 2\textsuperscript{nd} Consensus Conference on Neuraxial Anesthesia and Anticoagulation, 2002)

**QUICK REFERENCE GUIDE:**

Neuraxial Anesthesia in the Patient Receiving Thromboprophylaxis

<table>
<thead>
<tr>
<th>Medications</th>
<th>Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelet Medications:</td>
<td>No contraindication with NSAIDs; discontinue ticlopidine 14 d, clopidogrel 7 d, GP IIb/IIa inhibitors 8-48 h in advance</td>
</tr>
<tr>
<td>Unfractionated Heparin, SC</td>
<td>No contraindication, consider delaying heparin until after block if technical difficulty anticipated</td>
</tr>
<tr>
<td>Unfractionated Heparin, IV</td>
<td>Heparinize 1 h after neuraxial technique, remove catheter 2-4 h after last heparin dose; no mandatory delay if traumatic</td>
</tr>
<tr>
<td>LMWH, twice daily dosing</td>
<td>LMWH 24+ h after surgery, remove neuraxial catheter 2 h before first LMWH dose</td>
</tr>
<tr>
<td>LMWH, single daily dosing</td>
<td>First dose 6+ h after surgery, second dose 24+ h after the first dose. Neuraxial catheter may be safely maintained; catheter removed 10-12 h after LMWH and 2-4 h prior to next dose; postpone LMWH 24 h if traumatic</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Document normal INR after discontinuation (prior to neuraxial technique); remove catheter when INR ≤ 1.5 (initiation of therapy)</td>
</tr>
<tr>
<td>Thrombolitics</td>
<td>No data on safety interval for performance of neuraxial technique or catheter removal; follow fibrinogen level</td>
</tr>
<tr>
<td>Herbal Therapy</td>
<td>No evidence for mandatory discontinuation prior to neuraxial technique, be aware of potential drug interaction</td>
</tr>
</tbody>
</table>

For more detailed description of the ASRA guidelines, read the following pages.

**Regional Anesthesia in the Anticoagulated Patient: Defining the Risks**

**Introduction**

Patient management is based on appropriate timing of needle placement and catheter removal relative to the timing of anticoagulant drug administration. Familiarity with the pharmacology of hemostasis-altering drugs should guide the clinician in management decisions.

The consensus statements are designed to encourage safe and quality patient care, but cannot guarantee a specific outcome. The current information focuses on neuraxial blocks and anticoagulants; the risk following plexus and peripheral techniques remains undefined.
d. Monitor the patient postoperatively to provide early detection of motor blockade and consider use of minimal concentration of local anesthetics to enhance the early detection of a spinal hematoma.
e. Although the occurrence of a bloody or difficult neuraxial needle placement may increase risk, there are no data to support mandatory cancellation of a case. Direct communication with the surgeon and a specific risk-benefit decision about proceeding in each case is warranted.

3. Currently, insufficient data and experience are available to determine if the risk of neuraxial hematoma is increased when combining neuraxial techniques with the full anticoagulation of cardiac surgery. Postoperative monitoring of neurologic function and selection of neuraxial solutions that minimize sensory and motor block is recommended to facilitate detection of new/progressive neurodeficits.

4. The concurrent use of medications that affect other components of the clotting mechanisms may increase the risk of bleeding complications for patients receiving standard heparin. These medications include antiplatelet medications, LMWH and oral anticoagulants.

Anesthetic Management of the Patient Receiving Low Molecular Weight Heparin (LMWH)

All consensus statements contained herein respect the labeled dosing regimens of LMWH as established by the FDA. Concern remains for higher dose applications, where sustained therapeutic levels of anticoagulation are present.

1. Monitoring anti-Xa level is not recommended. The anti-Xa level is not predictive of the risk of bleeding and is, therefore, not helpful in the management of patients undergoing neuraxial blocks.
2. Concomitant administration of medications affecting hemostasis, such as antiplatelet drugs, oral anticoagulant, standard heparin, or dextran represents an additional risk of hemorrhagic complications perioperatively, including spinal hematoma. Education of the entire patient care team is necessary to avoid potentiation of the anticoagulant effects.
3. The presence of blood during needle and catheter placement does not necessitate postponement of surgery. However, initiation of LMWH therapy in this setting should be delayed for 24 hours postoperatively. Traumatic needle or catheter placement may signify an increased risk of spinal hematoma, and it is recommended that this consideration be discussed with the surgeon.
4. Preoperative LMWH
   a. Patients on preoperative LMWH thromboprophylaxis can be assumed to have altered coagulation. In these patients needle placement should occur at least 10-12 hours after the LMWH dose.
   b. Patients receiving higher (treatment) doses of LMWH, such as enoxaparin 1 mg/kg every 12 hours, enoxaparin 1.5 mg/kg daily, dalteparin 120 U/kg every 12 hours, dalteparin 200 U/kg daily, or tinzaparin 175 U/kg daily will require delays of at least 24 hours to assure normal hemostasis at the time of needle insertion.
   c. Neuraxial techniques should be avoided in patients administered a dose of LMWH two hours preoperatively (general surgery patients), because needle placement would occur during peak anticoagulant activity.
5. Postoperative LMWH
   Patients with postoperative initiation of LMWH thromboprophylaxis may safely undergo single-injection and continuous catheter techniques. Management is based on total daily dose, timing of the first postoperative dose and dosing schedule.
Ancrod

Overview

Ancrod (current brand name: Viprinex) is a defibrinogenating agent derived from the venom of the Malayan pit viper. The defibrinogenation of blood results in an anticoagulant effect. Currently, Viprinex®/ancrod is not approved or marketed in any country, but is being investigated as a stroke treatment in worldwide clinical trials. In January 2005, the U.S. FDA granted a 'fast-track status' for investigation of ancrod use in patients suffering from acute ischemic stroke, a life threatening condition caused by the blockage of blood vessels supplying blood and oxygen to portions of the brain, for which phase III trials are currently being conducted.

Marketing history

Under the brand name Arwin®, ancrod was marketed in Germany and Austria, where it was withdrawn in the 1980s after it was used for some decades. Arwin® was a brand name of Knoll Pharma. Neurobiological Technologies, Inc., currently holds the worldwide rights to ancrod under the brand name Viprinex®. Previously, the rights to Viprinex® were respectively held by Empire Pharmaceuticals, Inc., Abbott Laboratories, and Knoll AG, developers of this investigational drug.

Neurobiological Technologies, Inc. (NTI) has signed agreements with Nordmark Arzneimittel GmbH & Co KG (Nordmark) and Baxter Pharmaceutical Solutions, LLC (Baxter) to manufacture, fill and package Viprinex® for NTI's Phase III clinical trials in acute ischemic stroke. Nordmark will manufacture the biological active ingredient, ancrod. Date of this agreement was 1st. August 2005.

Chemistry and pharmacology

Ancrod has a triple mode of action. The exact structure and chemical data such as molecular weight are unknown, but it has been elaborated that the glycosylation of the molecule is an important factor. Glycosylation is remarkably homogenous with the major oligosaccharide accounting for approximately 90% of the total sugar content. Some in vitro reactions have been explored in very detail (see ref. #2, www.blckwell-synergy). Experimentally it was found that ancrod's actions are FAD dependent and that the substance has interesting apoptotic properties (causing programmed cell death), which still remain to be elaborated.

Ancrod is prepared from the crude venom of the Malayan pit viper (Agkistrodon rhodostoma, also termed Calloselasma rhodostoma) and belongs to the group of proteolytic enzymes. Ancrod may also be found in the venoms of many poisonous snakes (crotalids, elapids and vipers) in general, but the Malayan pit viper is most suitable due to a high concentration of ancrod in its venom. For its preparation a snake farm, very skilled and well trained staff (for milking the highly poisonous snakes), and special production facilities are required to purify the enzyme. The halflife of ancrod is 3 to 5 hours and the drug is cleared from plasma, mainly renally.

Due to its special mode of action (see below) and its price, Arwin® was never been used as 'normal' anticoagulant such as heparin, but only for the symptomatic treatment of moderate to severe forms of peripheral arterial circulatory disorders such as those resulting from years of heavy smoking and/or arteriosclerosis.

The substance is intended for parenteral, namely subcutaneous (s.c.) injection and intravenous (i.v.) infusion, and indirectly inhibits aggregation, adhesion, and release of thrombocytes mediated through the action of a fibrinogen degradation product (FDP). It also cleaves and therefore inactivates a significant part of circulating plasma fibrinogen. Fibrinogen is often found in increased concentrations in arteriae
APTT  (Activated Partial Thromboplastin Time)

CIGNA - Partial Thromboplastin Time

A longer-than-normal PTT or APTT can mean a lack of or low level of one of the blood clotting factors or another substance needed to clot blood.

A longer-than-normal PTT or APTT can be caused by liver disease, kidney disease (such as nephrotic syndrome), or treatment with blood thinners, such as heparin or warfarin (Coumadin).

The APTT is used to check treatment of people who are using heparin or other blood-thinning medicine to prevent blood clots.

Aptt argues that the criminal activity in this case was not extensive enough to qualify him for the four-level enhancement he received on his fraud offense for being the organizer or leader of criminal activity that involves five or more participants or is otherwise extensive.

Aptt, both Murphy brothers, and two other individuals were participants in the fraud offense, and therefore applied the four-level enhancement to Mr.

Aptt falsely represented to investors that "the houses [in Costa Rica] were being built in 21 days and sold very quickly," Mr.

The aPTT may be prolonged due to deficiency of one or more clotting factor or due to the presence of an inhibitor that interferes either specifically or nonspecifically with the measurement of a coagulation factor.

This is important because the aPTT tend to prolong upon incubation due to degradation of the labile clotting factors V and VIII.

The aPTT prolongs as the activated protein C in the patient’s plasma inactivates factors V and VIII on the reagent plasma.

The aPTT test measures the length of time (in seconds) that it takes for clotting to occur when
February 1996 - Heparin Monitoring

Heparin treatment is usually monitored to maintain the ratio of the patient's APTT to the mean control APTT within a defined range of approximately 1.5 to 2.5, referred to as the therapeutic range.

The therapeutic range for any given APTT reagent should therefore be established in the clinical laboratory to correspond to a heparin level of 0.2 to 0.4 U/mL by protamine titration.

Monitoring of heparin is difficult by conventional methods when the baseline APTT is prolonged as seen in patients with lupus anticoagulants and deficiencies of factor XII (Hagemen factor), prekallikrein (Fletcher factor) and high molecular weight kininogen (Fitzgerald factor).

www.itxm.org /Archive/tmu2-96.htm (1093 words)

Abstract

There are data suggesting that the activated partial thromboplastin time (aPTT) and anti-Xa activity that are used for monitoring UFH therapy in adults are not optimal in children.

The aPTT (Haemoliance Thrombosil, Beckman Coulter assayed on a MLA 1400) and anti-Xa activity (Haemoliance Anti-Xa chromogenic kit, Beckman Coulter assayed on MLA 1400) results from routine coagulation monitoring were collected prospectively.

The aPTT and anti-Xa levels do not correlate with UFH dose in children receiving therapeutic doses of UFH.


Hemostasis Reference Laboratory | Activated Partial Thromboplastin Time (APTT) with Kaolin

The APTT assesses the coagulation factors of the intrinsic pathway (factors XII, XI, IX, VIII, X, V, prothrombin, and fibrinogen).

The APTT will be prolonged in the presence of a factor deficiency, factor inhibitor, heparin or lupus-like inhibitors.

Shortening of the APTT can occur as a result of coagulation factor activation due to a traumatic venipuncture, inadequately processed sample, or disseminated intravascular coagulation (DIC).

www.psbc.org /lab_hemostasis/test01.htm (113 words)

A Critical Care Drug Update

In general, therapy with lepirudin is monitored using the aPTT ratio (patient aPTT at a given time over an aPTT reference value, usually median of the laboratory normal range for aPTT).

Any aPTT ratio out of the target range is to be confirmed at once before drawing conclusions with respect to dose modifications, unless there is a clinical need to react immediately.

Formation of antihirudin antibodies was observed in approximately 40% of HIT patients treated with lepirudin and this may increase the anticoagulant effect of lepirudin possibly because of delayed renal elimination of active lepirudin-antihirudin complexes.

www.continuingeducation.com /pharmacy/critical-care/anti-thromb.html (1162 words)

Refludan (Lepirudin) clinical pharmacology - prescription drugs and medications at RxList (Site not responding. Last check: 2007-10-26)

The pharmacodynamic effect of REFLUDAN on the proteolytic activity of thrombin was routinely assessed as an increase in aPTT.

For patients undergoing additional thrombolysis, elevated aPTT ratios were already observed at low lepirudin plasma concentrations, and further response to increasing plasma concentrations was relatively flat.
Deaths associated with platelet glycoprotein IIb/IIIa inhibitor treatment

D L Brown

Background: The glycoprotein (GP) IIb/IIIa inhibitors are potent antagonists of platelet aggregation that are approved to prevent thrombotic complications of percutaneous coronary intervention and for medical treatment of patients with acute coronary ischaemic syndromes. From safety data obtained from clinical trials, these agents appear to be associated with a definite but well tolerated increase in non-fatal bleeding complications. However, the bleeding risk of patients enrolled in clinical trials may not be representative of the population actually being treated with these agents.

Objective: To conduct a review of the adverse events related to GP IIb/IIIa inhibitors reported to the Food and Drug Administration (FDA).

Methods: 450 reports of death related to treatment with GP IIb/IIIa inhibitors were submitted to the FDA between 1 November 1997 and 31 December 2000. These were reviewed and a standard rating system for assessing causation was applied to each event.

Results: Of the 450 deaths, 44% were considered to be definitely or probably related to the use of GP IIb/IIIa inhibitors. The mean age of patients who died was 69 years and 47% of deaths occurred in women. All of the deaths deemed to be definitely or probably related to GP IIb/IIIa inhibitor treatment were associated with excessive bleeding. The central nervous system was the most common site of fatal bleeding.

Conclusions: Treatment with GP IIb/IIIa inhibitors may result in fatal bleeding complications in some patients. These findings suggest that patients treated in normal clinical practice may be at greater risk than those treated in clinical trials. Judicious use of these agents is therefore appropriate.

Methods

I requested, under the Freedom of Information Act, all adverse event reports filed with the FDA listing abciximab, eptifibatide, or tirofiban as the primary suspect drug. The Medwatch reports for the 450 adverse events resulting in death were then requested for further analysis. Causation was assessed using the following: an evaluation of the timing of the event in relation to the dose and duration of GP IIb/IIIa inhibitor treatment; an assessment of the pattern of response to determine whether it constituted a recognised reaction to GP IIb/IIIa inhibitor treatment; and determination of the contribution of any concomitant diseases, medical conditions, or other treatments.

In general, a death was considered definitely related to GP IIb/IIIa use when the precipitating causes of death coincided with the expected mechanism and duration of action of drug and no other drug likely to produce the same complication was being given. A death was defined as probably related to the use of GP IIb/IIIa inhibitors when the majority of the evidence supported the existence of a causal link but one or more aspects of the case were unknown or there was a minor inconsistency in the supporting evidence. Death was designated as possibly related to the use of GP IIb/IIIa inhibitors when it was equally likely that the death was not related to the GP IIb/IIIa inhibitor. Adverse event reports that included scant medical history and incomplete information about the drugs involved were considered to have insufficient evidence to assess causality. When the clinical course was highly inconsistent with known effects of GP IIb/IIIa inhibitors, the death was considered definitely unrelated.

Results

The age and sex of the patients who died following treatment with each of the GP IIb/IIIa inhibitors are given in table 1. Of the 450 deaths, 103 (23%) were associated with eptifibatide treatment, 143 (32%) with tirofiban, and 207 (46%) with abciximab. The median age of the patients who died was 70 years, with a range from 23–97 years. Women comprised 47% of patients who died. Overall, 27 deaths (6%) were thought to
Evaluation of the pharmacological properties and clinical results of the synthetic pentasaccharide (fondaparinux)

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Received 30 July 2002; received in revised form 13 January 2003; accepted 14 January 2003

Abstract

Fondaparinux (Arixtra®) is the first of a new class of selective indirect antithrombin-dependent factor Xa inhibitors, which inhibits thrombin generation. Fondaparinux is a completely synthetic pentasaccharide. It is a single molecular entity with a well-defined pharmacological target. Fondaparinux has nearly complete bioavailability after subcutaneous injection. The pharmacokinetics of fondaparinux appears predictable and consistent. The peak plasma level is obtained about 2 h after the subcutaneous injection, indicating that a rapid onset of antithrombotic activity is obtained on initiation of treatment. The elimination half-life is about 17 h and it is dose-independent, which allows a convenient once-daily dosing regimen. Fondaparinux is eliminated exclusively by the kidneys. Thus, the estimation of the renal function especially in elderly patients is important for the treatment with fondaparinux, whereas it is contraindicated in patients with severe renal insufficiency. Phase II clinical studies have identified a subcutaneous dose of 2.5 mg once daily for prophylaxis of venous thromboembolism in patients undergoing major orthopaedic surgery. Four phase-III clinical trials using bilateral phlebography for the diagnosis of DVT, demonstrated a combined 50% relative risk reduction of asymptomatic venous thromboembolic events in orthopaedic surgery patients in comparison to the low-molecular-weight heparin (LMWH) enoxaparin. Hemorrhagic complications for fondaparinux were either comparable or higher than those for LMWH but the authors did not judge that the increased bleeding was clinically relevant. A dose ranging study led to the selection of the dose of 7.5 mg at a single daily subcutaneous injection as optimal for the treatment of VTE. In two phase III clinical trials, the dose of 7.5 mg/day is expected to be as efficacious and safe as heparin for the treatment of DVT or PE, respectively. Phase II studies show that the efficacy-to-safety ratio of fondaparinux in the treatment of unstable angina or as an adjunct to thrombolysis in acute myocardial infarction is promising. These results demonstrated that a single anti-Xa agent devoid of antithrombin activity is a potent antithrombotic drug. Fondaparinux has obtained FDA and European health authorities approval. Its use on a large scale will allow the evaluation of its efficacy and tolerance in the daily clinical practice. Chemical modifications of the original synthetic pentasaccharide increase the affinity to AT resulting in a more potent inhibition of FXa and longer half-life. Idraparinux is the first of these new oligosaccharides that we named “meta-pentasaccharides.” After subcutaneous injection the half-life of idraparinux is about 80 h allowing a single injection per week. A dose-finding study has established the optimal dose given once a week to be compared with warfarin for the treatment of DVT.

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Keywords: Fondaparinux; Pentasaccharide; Antithrombin; Antithrombotic; Factor Xa inhibitor; Oligosaccharides

1. Introduction

The treatment of thrombotic disorders still remains a major challenge. Besides anti-platelet therapy, antithrombotic ther-

Abbreviations: AUC, area under the concentration–time curve; UFH, Unfractionated heparin; LMWHs, Low-molecular-weight heparins; VKA, vitamin K antagonists; TIMI, Thrombolysis in myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; VTE, venous thromboembolism; PE, Pulmonary embolism.

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Beyond Heparin and Aspirin

New Treatments for Unstable Angina and Non–Q-Wave Myocardial Infarction

Jeffrey I. Weitz, MD; Shannon M. Bates, MD

The goals of therapy for unstable angina and non–Q-wave myocardial infarction (MI) are to maintain myocardial perfusion by inhibiting platelet aggregation and fibrin deposition at sites of plaque rupture, thereby preventing ongoing or new myocardial ischemia and cardiac death. Although aspirin and heparin sodium are cornerstones in the management of unstable angina and non–Q-wave MI, both have significant limitations that have prompted the development of new agents. The thienopyridines, ticlopidine hydrochloride and clopidogrel, appear to be at least as effective as aspirin in the management of unstable angina. Glycoprotein IIb/IIIa receptor antagonists are a new class of platelet inhibitors that are more potent than aspirin, because they target the final common pathway of platelet aggregation. Low-molecular-weight heparins provide a more stable pharmacodynamic response and are more convenient to use than unfractionated heparin. Direct thrombin inhibitors show promise for inhibiting thrombin-mediated platelet aggregation and fibrin deposition. We focus on the opportunities presented by these agents, detailing mechanisms of action, advantages over aspirin and heparin, and performance in recent clinical trials.

Arch Intern Med. 2000;160:749-758

Patients with unstable angina pectoris are a heterogeneous group, encompassing those with progressive or accelerating angina and high-risk patients with angina at rest and reversible ST-segment changes on their electrocardiogram. Disruption of atherosclerotic plaque and superimposed thrombosis are fundamental steps in the pathogenesis of unstable angina. Rupture of the plaque exposes thrombogenic components, such as collagen, lipids, macrophages, tissue factor, and surface-bound von Willebrand factor, to intraluminal blood. Platelets adhere to exposed collagen and von Willebrand factor, where they become activated and recruit additional platelets by synthesizing thromboxane A2 and releasing adenosine diphosphate (ADP). Platelet activation induces a conformational change in glycoprotein IIb/IIIa (GPIIb/IIIa) that, by ligating fibrinogen, cross-links adjacent platelets. Exposure of blood to tissue factor in the necrotic core of the plaque activates the coagulation cascade and leads to the generation of thrombin. In addition to converting fibrinogen to fibrin, thrombin activates factor XIII, which stabilizes the fibrin clot. Thrombin also activates factors V and VIII, which promote further thrombin generation. A potent platelet agonist, thrombin activates platelets and contributes to the formation of a platelet-rich thrombus, the so-called white thrombus. Depending on the extent of activation of coagulation and the degree of stasis in the affected artery, a fibrin- and erythrocyte-rich thrombus (red thrombus) may develop and extend upstream or downstream from the ruptured plaque. Because white thrombus is typically labile, the thrombus may be degraded rapidly so that only partial occlusion of the lumen occurs, leading to unstable an-
chemical or enzymatic depolymerization. A pentasaccharide sequence randomly distributed along the heparin chains mediates the interaction between heparin and antithrombin. Binding of the pentasaccharide to antithrombin causes a conformational change in the latter, accelerating antithrombin-mediated inactivation of thrombin and factor Xa nearly 1000-fold. Because heparin catalysis of factor Xa by antithrombin does not require bridging between factor Xa and antithrombin, the smaller chains in LMWH retain their ability to catalyze factor Xa inhibition. Unfractionated heparin, therefore, has equivalent activity against factor Xa and thrombin, whereas LMWH exerts greater activity against factor Xa.

The LMWHs offer better bioavailability than does unfractionated heparin, because they bind less to plasma proteins and endothelium. Lack of both protein and cellular binding endows LMWHs with dose-independent clearance and a longer half-life, permitting once-daily subcutaneous dosing. These enhancements result in a more predictable anticoagulant response.

Although careful laboratory monitoring is essential with unfractionated heparin, no monitoring is necessary with LMWHs. It is probably best to avoid LMWHs in patients with significant renal dysfunction, because these drugs are cleared via the kidneys. Heparin-induced thrombocytopenia occurs less frequently with LMWHs than with unfractionated heparin, and LMWHs may also cause less osteoporosis than unfractionated heparin in long-term therapy.

Direct Thrombin Inhibitors

Unlike heparin and LMWHs, which act as anticoagulants by activating antithrombin, direct thrombin inhibitors act in an antithrombin-independent manner and bind directly to thrombin, thereby blocking its active site and preventing it from interacting with its substrates. The 2 direct thrombin inhibitors that have been studied most extensively are hirudin and bivalirudin. Both agents are bivalent inhibitors of thrombin that bind to the active and the substrate recognition sites (exosite 1) on thrombin. Hirudin forms a slowly reversible complex with thrombin and has a plasma half-life of 40 minutes after intravenous administration, and approximately 120 minutes after subcutaneous injection. Bivalirudin has a plasma half-life of 24 minutes after intravenous infusion. Unlike hirudin, bivalirudin produces only transient inhibition of the active site of thrombin and may, therefore, be safer. In contrast to heparin, direct thrombin inhibitors can inactivate fibrin-bound thrombin as well as free thrombin. Furthermore, they produce a more predictable anticoagulant response than unfractionated heparin. Of both agents, hirudin has been tested in patients with unstable angina and non-Q-wave MI, whereas bivalirudin has been studied as an alternative to heparin in patients undergoing PTCA, including patients undergoing PTCA for ongoing pain after a recent MI.

CLINICAL TRIALS

Thienopyridines

A randomized study, Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events (CAPRIE), compared aspirin (325 mg/d) with clopidogrel (75 mg/d) in patients with recent ischemic stroke, recent MI, or symptomatic peripheral artery disease. A total of 19,185 patients were enrolled in the study and were observed for 1 to 3 years (mean, 1.9 years). A total of 4059 of the participants withdrew from the study early, 21.3% in the clopidogrel and 21.1% in the aspirin groups, primarily because of adverse events. In those who remained in the study, the end point, a composite of ischemic stroke, MI, or vascular death, occurred in 5.3% of those given clopidogrel and in 5.8% of patients treated with aspirin. This translates into a relative risk reduction (RRR) of 8.7% ($P = .04$) with clopidogrel. Although this study indicates that long-term clopidogrel therapy is slightly more effective than aspirin therapy in patients with atherosclerotic disease, further studies are needed to define the role of clopidogrel in patients with unstable angina.

GPIIb/IIIa Antagonists

Four trials have evaluated GPIIb/IIIa antagonists in patients with unstable angina and/or non–Q-wave MI. One trial examined the utility of abciximab, another studied eptifibatide, and 2 trials studied tirofiban. Each is briefly described below.

The c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPRIE) study randomized 1265 patients with refractory unstable angina to abciximab or placebo starting 18 to 24 hours before PTCA and continuing until 1 hour after the procedure. All patients received aspirin and heparin. At 30 days, the primary end point, a composite of death, MI, or need for urgent intervention, occurred in 71 (11.3%) of 630 patients given abciximab, compared with 101 (15.9%) of 635 randomized to placebo ($P = .01$; RRR, 28.9%). Thrombocytopenia (platelet count, <100 x 10^9/L) occurred in 5.6% of those given abciximab and 1.3% of those receiving placebo. Although the rate of major bleeding episodes was low, major bleeding was more frequent in patients receiving abciximab than in those given placebo (3.8% and 1.9%, respectively; $P = .04$). Logistic regression analysis revealed that abciximab therapy and heparin dose per kilogram of body weight were significantly related to the risk for major bleeding.

During the 6-month follow-up, slightly more deaths occurred in patients who had received abciximab than in those randomized to placebo (2.8% and 2.2%, respectively), but MI occurred less frequently in those given abciximab compared with placebo (6.6% and 9.3%, respectively). The composite end point of death, MI, and need for revascularization occurred in 193 patients in both groups. Therefore, although abciximab significantly reduced the rate of MI before, during, and within the first few days after PTCA, it provided no significant benefit with respect to any of the outcomes after this period.
Direct Thrombin Inhibitors in Acute Coronary Syndromes
Present and Future

Jeffrey I. Weitz, MD; Harry R. Buller, MD, PhD

Most acute coronary syndromes are caused by intracoronary thrombus superimposed on disrupted atherosclerotic plaque. Platelets adhere to subendothelial proteins exposed at sites of plaque disruption where they become activated, release vasoactive and procoagulant substances, and aggregate. Tissue factor in the lipid-rich core of the plaque initiates coagulation, which leads to thrombin generation. A potent platelet agonist, thrombin recruits additional platelets to the site of vascular injury. Thrombin also converts fibrinogen to fibrin, which serves to stabilize platelet-rich thrombi formed at sites of plaque disruption. Depending on the extent and duration of coronary artery obstruction, clinical manifestations range from unstable angina to acute myocardial infarction.1,2

Aspirin and heparin, the cornerstones of therapy for acute coronary syndromes, reduce the risk of myocardial infarction and death.3,4 Despite the widespread use of these treatments, however, patients with unstable angina or acute myocardial infarction remain at risk for recurrent ischemic events, suggesting that intracoronary thrombus formation is incompletely attenuated by aspirin and heparin. High concentrations of thrombin are generated by tissue factor exposed at sites of arterial injury.4 When bound to fibrin,5,6 fibrin degradation products,7 or subendothelial matrix,8 thrombin is resistant to inactivation by the heparin/antithrombin complex. Bound thrombin, which remains enzymatically active, triggers thrombus growth by activating factors V, VIII, and XI,9 thereby amplifying thrombin generation. Bound thrombin also activates platelets,10 at least in part, via thromboxane A2-independent pathways that are not blocked by aspirin.

Because thrombin plays a central role in arterial thrombogenesis, the goal of most treatment regimens is to block thrombin generation or inhibit its activity. Direct thrombin inhibitors were developed to overcome the inability of the heparin/antithrombin complex to inactivate bound thrombin. In contrast to heparin and low-molecular-weight heparin, which catalyze the inactivation of thrombin by antithrombin,11,12 direct thrombin inhibitors bind to the enzyme and block its interaction with its substrates. This paper will outline the mechanisms responsible for protection of fibrin-bound thrombin from inhibition by the heparin/antithrombin complex, describe the potential advantages of direct thrombin inhibitors over heparin and low-molecular-weight heparin, review the clinical data with hirudin, bivalirudin (formerly known as Hirulog), and argatroban, and outline the opportunities and challenges for direct thrombin inhibitors in the face of new anticoagulant drugs currently under development.

Mechanisms of Protection of Fibrin-Bound Thrombin From Inactivation by the Heparin/Antithrombin Complex

Three distinct domains can be identified on thrombin.11 In addition to its active site, thrombin possesses 2 exosites, or positively charged domains located at opposite poles of the enzyme (Figure 1A). Thrombin uses exosite 1 to dock on its substrates, thereby orienting the appropriate peptide bonds into its active site cleft. Exosite 2 serves as the heparin-binding domain. To catalyze the inactivation of thrombin by antithrombin, heparin bridges the enzyme and the inhibitor by simultaneously binding to antithrombin and exosite 2 on thrombin. A unique pentasaccharide sequence found on one third of the chains of commercial heparin mediates its high affinity interaction with antithrombin.11

Thrombin binds to fibrin via exosite 1.14,15 By simultaneously binding to exosite 2 on thrombin and to fibrin, heparin bridges more thrombin to fibrin (Figure 2). Formation of this ternary heparin/thrombin/fibrin complex heightens the apparent affinity of the thrombin/fibrin interaction. When both thrombin exosites are ligated within this ternary complex, the enzyme is relatively protected from inactivation by the heparin/antithrombin complex.15 This protection reflects, at least in part, the inaccessibility of exosite 2 on thrombin within the ternary complex to antithrombin-bound heparin (Figure 1B). Thus, because exosite 2 is occupied by the heparin chain that tethers thrombin to fibrin, antithrombin-bound heparin is unable to connect the inhibitor to the enzyme. In contrast to the heparin/antithrombin complex, direct thrombin inhibitors can inactivate fibrin-bound thrombin (Figure 1C).

Direct Thrombin Inhibitors
Hirudin, bivalirudin, and argatroban are the 3 parenteral direct thrombin inhibitors currently approved by the US Food and Drug Administration. Hirudin and argatroban are li-
Native hirudin contains a sulfated tyrosine residue at position 63. Because recombinant hirudins lack this sulfate group, they are known as desulfatohirudins or desirudins. Native and recombinant hirudins bind to thrombin with high affinity, forming an essentially irreversible 1:1 stoichiometric complex with thrombin. Although desulfatohirudins bind thrombin with 10-fold lower affinity than hirudin, they remain potent inhibitors of thrombin.

The terminal half-life of desulfatohirudins in healthy volunteers is 60 minutes. Desulfatohirudins are cleared via the kidneys and accumulate in patients with renal insufficiency. Because no specific antidote is available to reverse their anticoagulant effect, desulfatohirudins should not be used in patients with impaired renal function.

**Bivalirudin**

A 20 amino acid polypeptide, bivalirudin is a synthetic version of hirudin (Table 1). Its amino-terminal D-Phe-Pro-Arg-Pro domain, which interacts with the active site of thrombin, is linked via 4 Gly residues to a dodecapeptide analogue of the carboxy-terminal of hirudin. Like hirudin, bivalirudin forms a 1:1 stoichiometric complex with thrombin. Once bound, however, the Arg-Pro bond at the amino-terminal of bivalirudin is cleaved by thrombin, thereby restoring active site functions of the enzyme.

Bivalirudin has a half-life of 25 minutes. In contrast to hirudin, renal excretion is not the major route of bivalirudin clearance. Instead, it is likely that bivalirudin is degraded by endogenous peptidases. Consequently, bivalirudin may be safer than hirudin in patients with renal impairment.

**Argatroban**

A synthetic small molecule, argatroban acts as a competitive inhibitor of thrombin. An arginine derivative, argatroban is approved as a heparin substitute in patients undergoing coronary angioplasty. Argatroban has a half-life of 12 minutes and, like bivalirudin, is not excreted by the kidneys. It is metabolized by the liver and bile. Argatroban is an effective inhibitor of thrombin in patients with impaired renal function.
placebo for an additional 72 hours, or to heparin given as a bolus plus infusion for 24 hours, followed by subcutaneous placebo injections for 72 hours. An additional bolus of placebo (in the hirudin group) or heparin (in those randomized to heparin) could be given if the procedure lasted longer than 1 hour, but no subsequent dose adjustments were allowed. The primary outcome was event-free survival at 30 weeks, defined as absence of death, myocardial infarction, coronary artery bypass grafting, or bailout angioplasty with or without coronary stenting at the previous angioplasty site.

At 7 months, event-free survival was similar in those given heparin, intravenous hirudin, or intravenous hirudin followed by subcutaneous hirudin (67.3%, 63.5%, and 68.0%, respectively). Likewise, on repeat angiography at 6 months, there was no significant difference in mean luminal diameter of the dilated vessel among the 3 groups. Compared with heparin, however, hirudin produced a significant reduction in the primary composite outcome at 96 hours (OR 0.61, 95% CI: 0.41 to 0.90) that was preserved at 30 days. The time-to-event curves converged thereafter, possibly reflecting the development of restenosis in both groups. No excess bleeding was seen with hirudin.

It is not surprising that hirudin failed to prevent restenosis because none of the antithrombotic agents tested to-date has influenced this process. The observation that hirudin was superior to heparin at 96 hours, and that this benefit was maintained at 30 days, is consistent with the results of other studies. In the OASIS-2 trial, 117 patients randomized to hirudin or heparin for unstable angina underwent percutaneous coronary intervention. At 35 days, hirudin produced a significant reduction in death or myocardial infarction compared with heparin (6.4% and 22.9%, respectively; OR 0.25, 95% CI: 0.07 to 0.86). Likewise, in the GUSTO-2B trial, 1404 patients received hirudin or heparin during percutaneous coronary interventions and for 72 hours thereafter. The risk of death or myocardial infarction was lower in the hirudin group than in those given heparin (2.1% and 3.8%, respectively; P=0.05). Thus, hirudin produces a greater reduction in death or myocardial infarction than heparin in patients undergoing coronary angioplasty, suggesting that potent antithrombotic drugs are needed to prevent thrombosis after mechanical injury to the coronary artery.

**Bivalirudin**

**Bivalirudin for Coronary Angioplasty**

Bivalirudin was compared with heparin in 4,098 patients undergoing coronary angioplasty for unstable or postinfarction angina. Bivalirudin did not reduce the primary endpoint, a composite of in-hospital death, myocardial infarction, abrupt vessel closure, or clinical deterioration of cardiac origin necessitating coronary intervention (OR 0.9, 95% CI: 0.8 to 1.1). Major bleeding, however, was significantly less frequent in patients randomized to bivalirudin than in those given heparin (3.8% and 9.8%, respectively; P<0.001). In a prospectively stratified subgroup of 704 patients with postinfarction angina, the primary endpoint occurred in significantly fewer patients receiving bivalirudin (OR 0.6, 95% CI: 0.40 to 0.90, P=0.004). Bleeding rates in this group were significantly lower with bivalirudin than with heparin (3.0% and 11.1%, respectively, P<0.001).

Despite these promising results, development of bivalirudin was temporarily halted. This decision was based on lack of clear evidence of superior efficacy in lower-risk patients. Although bivalirudin was safer than heparin, the initial process used to manufacture bivalirudin was complex, resulting in an expensive product. Consequently, there was an impression that the high cost of bivalirudin would limit its use in all but the highest risk patients.

A number of factors have changed the outlook for bivalirudin. By streamlining the manufacturing process, the cost of bivalirudin has now been reduced. Moreover, the decision to stop the development of bivalirudin was based on analysis of an incomplete data set because the original publication lacked information on some patients and follow-up was limited. A recent reanalysis of the results of the angioplasty trial suggests that bivalirudin is not only of benefit in the high-risk population, but also is superior to heparin in those at lower risk. Using the same closed database as the initial study, this reanalysis includes results on the entire intention-to-treat cohort of 4312 patients, as was specified in the initial protocol. In addition, it provides complete follow-up information and a more contemporary definition of myocardial infarction. When this additional information is included, bivalirudin significantly reduced the combined endpoint of death, myocardial infarction, or repeat revascularization in the entire cohort at 7 days (OR 0.78, 95% CI: 0.62 to 0.99, P=0.04) and at 90 days (OR 0.82, 95% CI: 0.70 to 0.96, P=0.01). Although the absolute risk reduction with bivalirudin at 180 days was similar to that at 7 days, the difference was no longer significant (OR 0.9, 95% CI: 0.78 to 1.04, P=0.15). Major bleeding events were significantly less frequent with bivalirudin than with heparin (3.5% and 9.3%, respectively; P<0.001).

Like hirudin, bivalirudin appears to be more effective than heparin in patients undergoing coronary angioplasty. However, bivalirudin reduces major bleeding compared with heparin. Some investigators have suggested that the dose of heparin used in the bivalirudin angioplasty trial was excessive, resulting in a higher than usual rate of bleeding in the control arm. Heparin was given as a 175 U/kg bolus followed by an infusion of 15 U · kg⁻¹ · h⁻¹ so as to achieve an activated clotting time (ACT) over 350 sec. An additional 60 U/kg heparin bolus was administered if the ACT was below this target. With this heparin regimen, the median ACT was 383 sec and the interquartile range was 332 to 450 sec. This result is close to ideal anticoagulation because a recent pooled analysis of data from 6 contemporary randomized trials indicates that an ACT of 350 to 375 sec with heparin produces the lowest rate of ischemic events at 7 days in coronary angioplasty patients not receiving glycoprotein (GP) IIb/IIIa antagonists. Moreover, the rates of major bleeding are not significantly greater in patients with a higher ACT than in those with a lower ACT.

**Argatroban and Other Active Site-directed Thrombin Inhibitors**

None of the active site-directed thrombin inhibitors has yet to undergo Phase III testing. In Phase II evaluation, argatroban
Comparison between tinzaparin and standard heparin for chronic haemodialysis in a Canadian center

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Two forms of heparin were used for haemodialysis. The first was unfractionated or standard heparin, with an average molecular weight of 15,000 Da. The second was low molecular weight heparin, with molecular weights varying between 1,000 and 10,000 Da, such as tinzaparin. Standard heparin was administered as an initial bolus of 50 to 75 units/kg (dry weight) followed by an infusion to maintain an activated clotting time (ACTESTER) between 150 and 200 seconds. The standard heparin infusion was discontinued 30 to 45 minutes before the end of dialysis. The initial dose of tinzaparin was 40 to 50% of the standard heparin dose. This was injected as a bolus in the arterial line at the beginning of haemodialysis.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised chronic adult haemodialysis patients. Patients with central venous catheters with a bleeding diathesis recorded as a significant episode of bleeding in the preceding 3 months were excluded. Also excluded were patients with thrombocytopenia (less than 150 x 10^9/L), patients with hepatic failure, and those receiving an oral anticoagulation regimen (mainly warfarin). However, patients taking an antiplatelet agent were not excluded.

Setting
The setting was a dialysis unit. The economic study was carried out at the Maisonneuve-Rosemont Hospital, Montreal, Canada.

Dates to which data relate
No dates or price year were reported.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was undertaken prospectively on the same patient sample as that used in the effectiveness analysis.
Laboratory Monitoring of Heparin and the Combination of Heparin and the Platelet Glycoprotein IIb/IIIa Receptor Antibody Fragment Abciximab (c7E3) in Patients Undergoing Percutaneous Transluminal Coronary Angioplasty (PTCA)

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**Background:** Previous studies in patients undergoing percutaneous transluminal coronary angioplasty (PTCA) have restricted laboratory monitoring to the activated clotting time (ACT). It remains unknown whether the ACT-prolonging effect of abciximab is clinically equivalent to a comparable degree of anticoagulation by heparin.

**Patients and Methods:** 30 patients undergoing PTCA received 100 IU of heparin/kg body weight. Another 30 patients received an initial bolus of 70 IU of heparin/kg + abciximab. We determined ACT, laboratory and on-site activated partial thromboplastin time (APTT) and plasma heparin levels.

**Results:** Despite markedly different preintervention heparin dosing, the ACTs were not significantly different between groups. After termination of PTCA, the median ACTs of both study groups were nearly equivalent (267 vs. 272 s; p = 0.79). The median ACT-prolonging effect of abciximab could be equated with 0.68 IU/ml heparin. Both APTT assays were not suitable for monitoring the anticoagulant effects during PTCA due to their high sensitivity. By contrast, the plasma heparin levels clearly reflected the different heparin doses. The weak correlation (r = 0.23) between ACTs and heparin levels in patients receiving heparin + abciximab was due to excessively prolonged ACTs in six patients (540–1,245 s). These data could be attributed to an unusually high response to abciximab. By contrast, the ACT was a reliable measure of the anticoagulant effect of heparin in patients receiving exclusively heparin.

**Conclusions:** ACT reflects both heparin and abciximab therapy, whereas heparin levels reflect only heparin dose. The APTT assays were not suitable for monitoring the anticoagulant effects during PTCA.

**Key Words:** Angioplasty · Heparin · Abciximab · Hemorrhage

**Herz 2003;28:445–52**
DOI 10.1007/s00059-003-2349-3
Low Molecular Weight Heparin and Neuraxial Anesthesia
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Abstract
Spinal and epidural anesthesia/analgesia provide several advantages over systemic opioids, including superior analgesia, reduced blood loss and need for transfusion, and decreased incidence of thromboembolic complications. However, patients hospitalized for major surgery often receive an anticoagulant and/or antiplatelet medication perioperatively to prevent venous thrombosis and pulmonary embolism, although the pharmacologic agent, degree of anticoagulation desired, and duration of therapy remain controversial. These patients are often not considered candidates for spinal or epidural anesthesia/analgesia because of a theoretically greater risk of spinal hematoma. Spinal hematoma is a rare and potentially catastrophic complication of spinal or epidural anesthesia. The incidence of neurologic dysfunction resulting from hemorrhagic complications associated with central neural blockade is estimated to be less than 1 in 150,000 epidural and less than 1 in 220,000 spinal anesthetics. The decision to perform neuraxial blockade on these patients must be made on an individual basis, weighing the risk of spinal hematoma from needle or catheter placement against the theoretical benefits gained. Familiarity with the pharmacology of hemostasis-altering drugs, as well as case reports and clinical studies involving patients undergoing neuraxial blockade while receiving these medications will guide the clinician faced with this difficult decision. © 2001 Elsevier Science Ltd. All rights reserved.

Key Words: Regional anesthesia; Complications; Spinal anesthesia; Epidural anesthesia; Spinal hematoma; Low molecular weight heparin

Spinal hematoma is a rare and potentially catastrophic complication of spinal or epidural anesthesia. Within 10 years of the first spinal anesthetic, administered by Bier in 1898, the first spinal hematoma following neuraxial blockade was recorded. Usubiaga [1] reported permanent paralysis in a 36-year-old male after unsuccessful spinal anesthesia for excision of a pilonidal cyst. Ten days later, the patient complained of paresthesias and weakness of his lower extremities. Lumbar radiograph demonstrated spina bifida occulta, while dilated spinal veins consistent with a vascular tumor were noted during decompressive laminectomy. Neurologic recovery was poor. Although there was no evidence for a preexisting coagulopathy, the spina bifida occulta and vascular malformation were regarded as risk factors contributing to the development of spinal hematoma. Patients with preexisting coagulopathies have historically been considered at increased risk for hemorrhagic complications following neuraxial blockade. In 1953, the first spinal hematoma in a patient with altered hemostasis was noted by Bonica [2]. The patient complained of signs consistent with cauda equina syndrome 4 days after bloody spinal puncture. Exploratory laminectomy revealed extensive clots within the subarachnoid space, which were compressing the conus medullaris. Hemostasis was difficult due to continued...
REFLUDAN was the first direct thrombin inhibitor (DTI) to be approved by the Food and Drug Administration (in 1998) for anticoagulation in patients with heparin-induced thrombocytopenia (HIT) and associated thromboembolic disease in order to prevent further thromboembolic complications (TECs). It is a recombinant hirudin, a derivative of the saliva of the medicinal leech *Hirudo medicinalis*. To date, nearly 60,000 patients have been treated with REFLUDAN worldwide.

REFLUDAN is a bivalent, highly potent and specific direct inhibitor of both circulating and clot-bound thrombin, and has proved to be an effective and safe anticoagulant therapy for patients with HIT. It promotes rapid recovery of platelet counts, provides effective anticoagulation, and prevents further thromboembolic events.

The principal trials for REFLUDAN were HAT-1 and HAT-2, two prospective, multicenter, historically controlled clinical studies in patients with serologically confirmed HIT. By Day 35 in the HAT-1 study, the REFLUDAN group showed a relative reduction of the cumulative risk for combined clinical endpoints (death, limb amputation, and new TECs) by 73% vs historical controls. A meta-analysis of the HAT-1 and HAT-2 studies confirms a statistically significant difference in the combined incidence of death, new TECs, and amputations in favor of REFLUDAN vs historical control in patients with TECs. Relative risks for individual events also decreased.

The most frequently occurring adverse event in clinical trials was bleeding. With REFLUDAN, the most common adverse events were bleeding from puncture sites and wounds (14%), anemia (13%), and hematoma (11%). As with other anticoagulants, hemorrhage can occur at any site in patients receiving REFLUDAN. There have been reports of intracranial bleeding with REFLUDAN in the absence of concomitant thrombolytic therapy. Serious anaphylactic reactions that have resulted in shock or death have been reported during initial administration or upon second or subsequent re-exposure.

**Historical Background of Hirudin**

The name hirudin is derived from *Hirudo medicinalis*, the medicinal leech used since antiquity in the practice of blood-letting, or phlebotomy. As the leech fastens onto the patient’s skin, its salivary glands secrete a powerful anticoagulant that prevents the blood clotting that would deprive the leech of its meal.

In 1884, John Haycraft, who was working in a pharmacology laboratory in Strasbourg, was able to demonstrate that leeches contained a substance with anticoagulant properties. Until the discovery of heparin, this substance was the only means physicians had to prevent blood from clotting. Finally, in the late 1950s, attempts to isolate the anticoagulant agent in leech saliva were successful, and hirudin was named and classified as a thrombin inhibitor. In 1976, the primary chemical structure of hirudin was established. A number of difficulties arose, however, in isolating hirudin from medicinal leeches. A limited number of leeches was available due to the failure of breeding trials, and leeches were placed on the endangered species list.