Chapter 12

Essential Direct Thrombin Inhibitor Knowledge

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Chapter Outline

Introduction

When vascular injury occurs, proenzymes and procofactors are converted into active substances that work in concert to generate thrombin as part of the hemostatic repair process. Thrombin has a central role in this process as both a procoagulant and anticoagulant. Thrombin regulated procoagulation includes conversion of soluble fibrinogen to fibrin, activation of factors V, VIII and XIII; increasing formation of fibrin cross linking and clot stabilization.[1-3] Process that causes activation of thrombin can lead to undesirable arterial or venous thromboembolism. Inactivation of thrombin may eliminate its ability mediate additional thrombus formation.

Pharmacology

The activity of thrombin can be inhibited by currently available agents that bind directly to either the catalytic or active site, substrate recognition site (exocite 1), or heparin-binding site (exocite 2). Unfractionated heparin (UFH), low molecular weight heparin (LMWH) and fondaparinux are considered to be indirect anticoagulants because of their ability to catalyze the inhibitory effects of antithrombin (AT) against thrombin. When heparin binds simultaneously to exocite 2 and AT, a heparin-thrombin-antithrombin complex is formed. Heparin can also act as a bridge between fibrin and thrombin via exocite 2. The occupation of both sites on thrombin protects the enzymatic activity from inactivation but reduces its ability to inhibit thrombin already bound to fibrin and thrombus growth.[1]

In contrast, direct thrombin inhibitors (DTI) bind directly to the catalytic region on thrombin responsible for enzymatic activity. Binding to the catalytic region or active site on thrombin inhibits several of the actions of thrombin including platelet activation and cleavage of fibrinogen involved in thrombus formation. The bivalent DTIs (lepirudin and bivalirudin) also bind to the substrate recognition (exocite 1) on thrombin where fibrinogen can bind. Since the DTIs do not bind to exocite 2, they are capable of inhibiting the effects of thrombin already bound to fibrin (clot bound thrombin). Direct thrombin inhibitors can also block throm-

bins ability to activate platelets, stimulate granule release, surface receptor expression and aggregation in addition to a plethora of other factors that mediate vascular integrity.[2]

Pharmacokinetics/ Pharmacodynamics

Currently, three parenteral DTIs are available in U.S.: bivalirudin, lepirudin, and argatroban. Notable pharmacokinetic and pharmacodynamic differences between the three agents result in agent specific dosing regimens and effects on clot based laboratory assays (Table 12-1).

Lepirudin

The first DTI to become available in the U.S. was lepirudin, a recombinant product derived from leech (Hirudo Medicinalis) saliva, which has been observed to have anticoagulant properties since 1884. Of the three DTIs, lepirudin has the tightest binding to thrombin, with a dissociation constant around 2×10^{-14} M. Because of the low dissociation constant, lepirudin can inhibit thrombin at a very low concentration compared to the other DTIs.[3] The inhibition of thrombin can also continue for up to 18 hours after administration. The kidney is the primary site for removal of lepirudin, accounting for 50%–60% of clearance with additional elimination via the bile and liver. Pharmacokinetic studies have observed an elimination half-life of approximately 1.3 hours in healthy subjects with normal renal function, which can be prolonged as creatinine clearance (CrCl) decreases.[2]

Bivalirudin

Bivalirudin is a recombinant analog of hirudin that has the most rapid elimination rate of the three DTIs, having a half-life of approximately 30 minutes with 20% eliminated unchanged in the urine in healthy controls.[2] The dissociation constant of bivalirudin is approximately 1.9 nM. In patients receiving bivalirudin for PTCA, serum concentrations correlated with measured aPTT values.[2] Bivalirudin is inactivated by enzymatic cleavage of the Arg–Pro bond in the amino-terminal domain by thrombin itself in addition to dissociating from the thrombin complex, allowing thrombin to recover its activity.[2] Because of the enzymatic cleavage by thrombin, the reduction in dosing of bivalirudin may not be as notable as lepirudin or argatroban in patients with reduced renal or hepatic function, respectively.[4] Because of thrombins ability to enzymatically inactivate bivalirudin, pooled blood in the field outside the circulation (during surgery), or in a cell-saver reservoir may be prone to clotting.[5] Reduced dosing has been suggested when renal insufficiency is present; however, the dose may need to be subsequently increased during hemodialysis, as hemofiltration has been shown to remove bivalirudin.[6-8]

Argatroban

Argatroban is a synthetic derivative of arginine that selectively inhibits only the active site on thrombin, with a dissociation constant of 3.9×10^{-8} mol/L.[2] Argatroban can effectively inhibit the activity of circulating and bound thrombin.[2,9] It is primarily eliminated hepatically, with an elimination half-life in healthy control subjects of 31–51 seconds. A notable increases in the elimination half-life was observed in the presence of mild to moderate hepatic insufficiency.[10]

Concurrent agents such as aspirin have not been observed to alter the elimination of DTIs. It should be noted that clinical trials have typically excluded patients with liver or renal impairment, and thus the true pharmacokinetic to pharmaco-

Table 12-1. CD

Pharmacokinetics of Available Antithrombin Agents[11-13]

Agent	Argatroban	Bivalirudin	Lepirudin
Route of administration	IV	IV	IV/SC
Plasma half-life normal subjects	39–51 min	10–24 min	1.3 hours
Primary elimination route	Hepatic	Enzymatic	Renal
Fraction excreted unchanged in the urine (Fe)	16%	20%	35%

dynamic responses in these patients as not been established.

Indications

Lepirudin and argatroban are indicated for anticoagulation therapy in the setting of prophylaxis or treatment of thrombosis in heparin induced thrombocytopenia (HIT). Argatroban and bivalirudin are indicated for patients with HIT requiring percutaneous coronary intervention (PCI). Bivalirudin is also indicated in the setting of unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA) or PCI in non-HIT patients.[11-13]

DTIs in HIT

Because HIT was a catastrophic disease without an approach for management, the parenteral DTIs were not extensively studied in dose ranging phase II trials. Instead, clinical trials comparing argatroban or lepirudin to a historical were undertaken simultaneously as it was determined that a blinded randomized control trial would be unethical. The argatroban trial was predominantly done in North America, selecting an aPTT target range of 1.5 to 3 times control. In contrast, lepirudin was investigated in Germany with an aPTT target of 1.5 to 2.5 times control. Because of the numerous differences in the populations studied including the duration of DTI therapy, degree of thrombocytopenia, or confirmation of antibody test, it would be difficult to directly compare observed results between the two agents for differences in efficacy or complication rates. Some notable observations from the trials however continue to influence how clinicians use these agents in the management of HIT.

Of the three parenteral DTIs, lepirudin has an elimination half-life long enough to facilitate administration by the subcutaneous route. A linear dose response in the aPTT was observed with SC lepirudin, 0.75 mg, 1.25mg and 2 mg SC every 12 hours over a 5 day period in initial management of DVT.[14] In the setting of HIT, case studies have suggested 25-50mg SQ ever 12 hours can prevent thrombosis complications after initial management with a DTI infusion.[15-17] Outside HIT, DTIs may offer an alternative approach to anticoagulation when antithrombin deficiency or concerns for hypersensitivity to heparin are present.

Initiating a DTI Infusion

The initial dosing regimen for a DTI will depend on the indication for anticoagulation, clinical presentation of the patient, and the desired intensity of parenteral anticoagulation, as is also the case with the use of heparin. In the setting of HIT, antithrombin deficiency or treatment of thromboembolic complications, a lower intensity of anticoagulation is targeted compared to treatment of acute coronary syndrome. The initial dose may depend on the presence of thrombosis, impaired organ function and presence of active bleeding or risk factors for bleeding (Table 12-2).[8] When concerns for bleeding are present in the absence of thrombosis, the lower end of the reduced intensity target range may be considered. In the presence of acute thrombosis and limited risk for bleeding, the higher end of the target range may be considered.

Table 12-2. CD

Steps in the Initiation, Monitoring, and Transition Off DTI Therapy

Initiating DTI therapy

1. Draw baseline aPTT and INR if not previously done.
2. Evaluate renal, liver and cardiac function for potential reasons to reduce the dose.
3. Initiate DTI depending on target goals and indication for use.
   a. Consider a regimen with a sliding scale in mg/h for simplicity
   b. Consider a simple standard dilution (1 mg/mL) and rates in "mg/h" if possible to decrease confusion in administration rates and charting.

Monitoring the DTI infusion

1. Draw aPTT at a predetermined time within 2–6 hours to reduce the risk of over-targeting or under-targeting the selected aPTT goal.
   a. Adjust upwards any value notably below a ratio of 1.5 × baseline.
   b. Consider adjusting downward if the upper end of the target range, or above prior to achieving steady state.
   c. Follow platelet count, patient and HCT (or hemoglobin) for any evidence of bleeding.
2. If an INR is requested, consider including an aPTT to determine amount of DTI effect on the INR value.

For lepirudin, the initial starting dose in isolated HIT (thrombocytopenia without acute thrombosis) is 0.1 mg/kg/h with no bolus.[18-19] In a meta analysis of the three primary lepirudin trials, the mean dose in this setting was 0.06 mg/kg/h.[20] If acute thrombosis is present, than a bolus of 0.4 mg/kg followed by a infusion of 0.15 mg/kg/h is suggested. Since lepirudin is primarily eliminated via the kidney, a dose reduction is suggested as renal function declines based on reliable methods for estimating function.[12,21-22] Subsequent analysis of dosing in the clinical trial in addition to independent observations suggest that a trend towards doses lower then provided in the prescribing information are fairly common.[23-24] This might be attributed to the identified target range, sensitivity in the aPTT assay, use in sicker patients and influence of reduced cardiac, hepatic or renal function.

In patients requiring hemodialysis, the half-life of lepirudin was observed to be 30 times longer (51.8 ± 15.6 hours) than observed in a normal renal function control comparator (1.7 ± 1.5 hours).[25] In patients with severe renal dysfunction, removal and dosing adjustment may depend on the degree of residual renal function observed by current urine output.[26] Lepirudin can be removed to some extent during hemodialysis, with potentially greater elimination observed when dialyzers with a greater negative charge on the membrane surfaces are used.[22, 27] Antibodies to lepirudin that can reduce clearance have been observed with prolonged use.[28]

The elimination half-life of lepirudin administered subcutaneous is approximately 4 to 8 hours with peak observed 1.3–2.5 hours post the dose, allowing effective anticoagulation using twice daily dosing.[29] In a dose-ranging analysis comparing twice daily SC lepirudin to heparin in the treatment of proximal DVT, a linear response in aPTT was observed between 0.75 to 2 mg/kg.[14] The 1.25 mg/kg lepirudin dose was just as effective as heparin, with fewer adverse effects compared to the higher 2 mg/kg dose. Measured aPTT ratio values prior to a dose were between 1.5 and 2.0, and peak (3 hours post injection) approximately 2.2 and 2.7 times control. Peak levels 2 hours post administration targeting an aPTT ratio of approximately 2–2.5 times control showed no evidence of accumulation over the 2–3 weeks.[15]

For argatroban, the initial starting dose for treatment of HIT was 2 mcg/kg/min, with a mean dose maintenance infusion of 1.6 to 1.7 mcg/kg/min observed in the clinical trials.[30-32] Lower mean doses than observed in clinical trials have been described in reports from individual institutions.[23-24] Since argatroban is hepatically eliminated, the dose should be reduced to 0.25 mcg/kg/min in patients with mild to moderate liver failure.[10] In patients with major hepatic failure, lower doses and very prolonged effects have been observed.[33-34] Argatroban is eliminated to a limited extent renally. Initially, this was considered to be insignificant, and no alteration in dosing was recommended based on observations in the clinical trials.[11,35] Subsequent reports describe requirements for lower infusion rates depending on the degree of renal insufficiency.[36-38] In one report, the mean argatroban maintenance dose to maintain an aPTT value of 60 seconds was 2.2 ± 0.34 mcg/kg/min for creatinine clearances over 60 ml/min, 1.2 ± 0.15 mcg/kg/min for creatinine clearance of 31–60 mL/min and 0.8 ± 0.4 mcg/kg/min for creatinine clearance below 31 mL/min were observed.[38] Unlike lepirudin or bivalirudin, argatroban is not eliminated during hemodialysis, making it unnecessary for any dosing adjustments.[33,39]

As with heparin, a higher degree of anticoagulation may be necessary in selected situations such as bypass surgery or coronary intervention. The DTI dose may depend on use of other concurrent medications such as a glycoprotein IIb/IIIa inhibitor in PCI, or if on pump or off pump coronary bypass surgery is undertaken. For cardiac bypass surgery, dosing approaches may include a selected bolus dose, infusion rate of the subsequent DTI, preservation of the cell saver; and timing of infusion discontinuation. In these settings, a planned dosing approach should consider available trials and the perspective agent chosen. As the result of reduced cardiac output of transient hypoperfusion to the kidney or liver during surgery, a reduced DTI dose may achieve target goals postoperatively. As cardiac function and perfusion increases in subsequent days, the infusion rate may need to be increased.

Contraindications/Precautions

In clinical trials for any anticoagulant, the efficacy of primary and secondary outcomes is typically influenced by the incidence of minor, major and life-threatening bleeding. Unfortunately, no standardized definition of bleeding in either category exists, and there are no well-controlled direct comparisons between the different DTIs. Current dosing strategies have evolved as appreciation for renal function or hepatic function in post marketing analysis or reports from individual centers recognized a need to adjust the dose downward, potentially reducing in the risk for bleeding. Since the DTIs are dosed differently in both HIT and ACS, the incidence of bleeding may depend on which setting they are being used.

In the initial lepirudin trials for treatment of HIT, major bleeding was associated with higher aPTT values (67 to 79 seconds) compared to 47 to

Clinical Pearl

In severe renal impairment, argatroban may be preferred secondary to its hepatic elimination and pharmacokinetic and pharmacodynamic evidence suggesting no alteration of elimination in hemodialysis.[40]

60 seconds without any difference in the rate of thrombotic complications.[40-43] As the relationship between renal function and initial lepirudin dosing became apparent, the incidence of excessive values and bleeding declined. In a post marketing analysis of the use of lepirudin, not only was a lower incidence of both limb amputations and new thrombotic complications observed, but also a 3-fold reduction in major bleeding from the original trials.[44] Recent analysis of the original argatroban trial and two subsequent trials demonstrated a similar rate of major bleeding between argatroban and control patients.[45]

Overall, the reductions in both thromboembolic and major bleeding can be attributed in part to increased familiarity with the use of these agents; however, voluntary reporting may have reduced the proportion of negative results. Prior to starting a DTI, the benefits of thrombosis management should be balanced with the risk for bleeding when developing a management plan. Considerations may include the desired intensity of anticoagulation.

An important challenge with the DTIs is the lack of a reversal agent. The relatively short half-life in the absence of organ dysfunction may reduce their potential ability to inhibit formation of a fibrin plug for prolonged periods of time. In patients at risk for bleeding, selecting the DTI with the shortest half-life after assessing renal and hepatic function may reduce challenges in controlling any bleeding events. Such may be the case when patients require invasive procedure, are intubated with risk for tracheal trauma, or have open wounds where excessive bleeding is not desired.

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Acutely ill patients such as those with renal, hepatic or cardiac dysfunction may reach target aPTT values at doses notably lower than observed in the clinical trials. Alterations in dosing requirements may be necessary as the dynamic clinical presentation of the patient changes. Measured aPTT values should take this under consideration to adapt infusion rates, and prevent under or overshooting target goals.

Hypersensitivity

Antibodies to lepirudin have been reported to form during prolonged infusions resulting in a greater aPTT response, leading to lower infusion rates.[46] There was no correlation with the presence of antibodies and incidence of amputations, thrombotic complications and major bleeding. Separately, anaphylactic reactions (0.015%) are reported, with a higher yet still rare occurrence (0.16%) for a severe reaction if there has been a previous exposure to lepirudin in recent months.[47-48] Epitopes on bivalirudin may recognize antibodies to lepirudin, however, any clinical significance for this is unclear.[49] Any previous exposure to either lepirudin or bivalirudin should be incorporated in the process of agent selection. Patients with a history of exposure to lepirudin should be monitored for potential, albeit rare, symptoms of a hypersensitivity response, which may include an unexplained need to alter the infusion rate to maintain the targeted degree of anticoagulation. All three DTI are contraindicated in patients with known hypersensitivity to the DTI involved.

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Differences in sensitivities for aPTT reagents between heparin or DTI can occur, and thus the target aPTT range for a DTI may not be the same as heparin for a particular reagent and may very between institutions with different aPTT assay.

Monitoring

The laboratory parameters to measure the degree of anticoagulation may depend on the situation and desired intensity of anticoagulation. Generally, the aPTT is used for management of HIT or treatment of a venous or peripheral arterial thromboembolism. The intensity of anticoagulation with a DTI in the setting of HIT is an aPTT ratio for bivalirudin or lepirudin of 1.5 to 2.5 times the

Clinical Pearl

The choice for an initial DTI dose may depend on the setting, risk or presence of acute thrombosis, and, separately, bleeding. During use in coronary interventional therapy, this may be confounded by the addition of parenteral antiplatelet agents, or when using the activated clotting time (ACT) used for any adjustment in the infusion rate. In the setting of HIT, the aPTT is typically used, targeting the lower end of the aPTT range if bleeding risk is high and risk for thromboembolism low. The higher end of the range is targeted if bleeding risk is low and acute thromboembolism (or high risk for one) is present.[2]

patient's baseline value (lepirudin, maximum of 100 seconds), or 1.5 to 3 times baseline with argatroban based on the endpoints set in the original trials. In the absence of a baseline aPTT value, then the laboratory median normal aPTT value can be considered. The upper end of the targeted range may be considered when the risk of thrombosis far exceeds concerns for bleeding. In contrast, the lower end of the target range may be desired when notable bleeding concerns such as recent surgery, intubation, open wounds, or recent major bleeding as examples are present. However, the importance of maintaining an aPTT ratio above 1.5 should be noted, as frequent values below has been associated with increased risk for thrombosis.[20] To avoid aPTT values below the target range, a slightly higher low end ratio goal above 1.5, such as 1.6 to 1.8, may be a consideration.

Since the mechanism of DTIs and sensitivity of the aPTT assays are different than UFH, the intensity of anticoagulation and target range for a given aPTT value may be different. Thus, target aPTT ranges for either agent (heparin and separately a DTI) to a given assay should be independent of each other.[50] The sensitivity of the aPTT to a given DTI concentration may also vary between reagents.[51] An additional note is that a flattening of the aPTT dose response curve has been observed at higher degrees of anticoagulation intensity with minimal change in the aPTT as the DTI concentration increases.[19] The activated clotting time (ACT) may be used in situations where a higher degree of anticoagulation may be required, such as invasive cardiac or selected surgical procedures (i.e., coronary intervention, coronary bypass or ECMO). Given that higher DTI doses are used, excessive INR result may be observed in these settings if measured.

Once the DTI infusion is started in the setting of HIT, an aPTT should be drawn within 2-6 hours depending on the need for aggressive anticoagulation or concerns for bleeding to determine if an adjustment in dosing is needed to achieve target goals (Table 12-2). Frequently, patients requiring

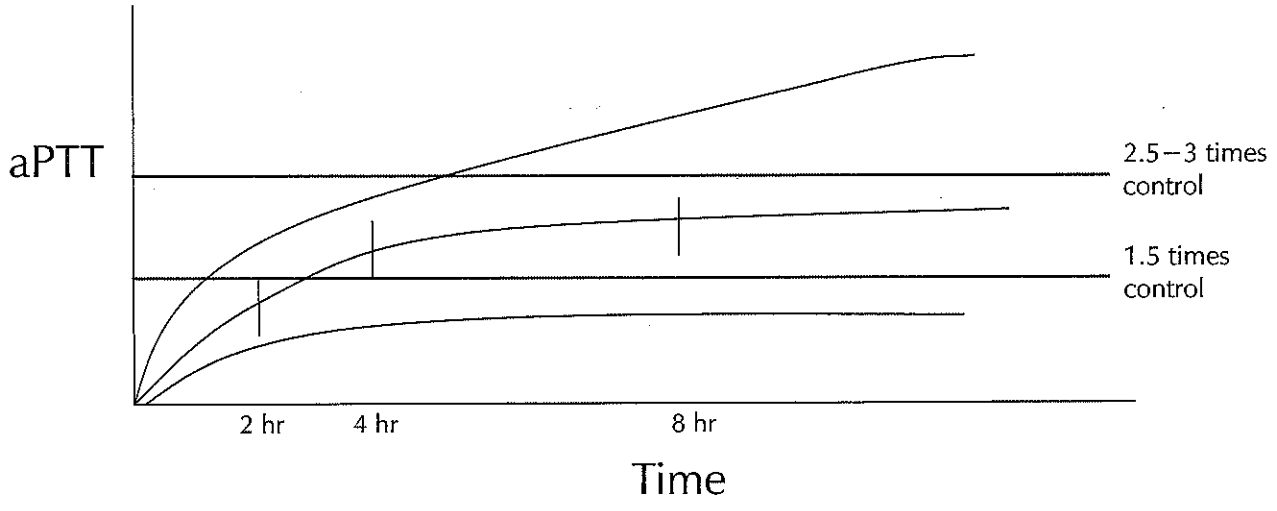


Figure 12-1. If clearance of the DTI is reduced, steady state may not occur for an extended period of time. Measuring the aPTT prior to steady state may assist in determining if the rise is too rapid, even if it is within the target range, or so small that an increase in the infusion rate may be necessary. Waiting to draw the aPTT at steady state may create the risk of prolonged periods time above or below the target range.

DTI therapy have longer elimination half-lives than observed in healthy subjects. As such, the time to steady state can be notably longer, especially if hepatic, renal or impaired cardiac function is present.[8,33,52-54] Waiting for steady state prior to checking an aPTT value may also be to late to avoid undesirable low or excessive values. Checking an aPTT earlier may assist in showing the trend of rise, and allow for any necessary rate adjustment (Figure 12-1). Once steady state has been achieved, the infusion rate can also assist in suggesting how long the effects of the DTI will last once the infusion is discontinued. A low dose DTI regimen achieving target aPTT values may suggest reduced clearance and a longer time for the effects of the DTI to dissipate once stopped. All three DTIs can falsely increase measured INR values in the clinical laboratory, with the most notable effects with argatroban followed to a lesser extent by bivalirudin and lepirudin.[55]

Transitioning to Warfarin

In situations where prolonged anticoagulation is needed, therapy may transition to an anticoagulant more suitable for long-term management. In the case of warfarin, this is a unique challenge because of the DTIs ability to independently elevate the INR. The elevated INR is primarily an in-vitro effect that occurs in the laboratory, and does not, at least for argatroban, reflect an elevated degree of anticoagulation in the patient.[56] Clinicians should thus be cautious not to stop a DTI infusion in the absence of warfarin because of a elevated INR value. Both the DTI concentration and higher international sensitivity indexes (ISI) values of the test can also influence the observed rise in the INR.

In the setting of HIT, warfarin therapy should not be initiated until target aPTT values with the DTI are achieved, and the platelet count is under sufficient recovery. A minimum of 5 days overlapping DTI and warfarin therapy and adequate recovery in platelet count in the setting of acute HIT is also recommended.[57] To avoid the potential for warfarin related venous limb gangrene associated with HIT, warfarin should be initiated cautiously (lower dose) to avoid early excessive anticoagulation while DTI therapy is continued until adequate platelet count recovery has occurred. This may be difficult to determine when a mixed source of thrombocytopenia is present (lack of rise in the platelet count), or suspicion that HIT was not present. Since presence of a DTI can increase the INR, and warfarin the aPTT, determining the degree of anticoagulation independently for either agent when both are present can be difficult.[55,58] Selected parameters have been suggested, however, the multiple variables in assays and their sensitivities can make application of these approaches difficult.

One approach to determine if the target INR for warfarin has been reached is to start with a baseline INR on DTI therapy alone once target aPTT values are achieved (Table 12-3). When the aPTT is stable and the INR value after 5 days of therapy has risen 1.5 to 2 times with minimal change in the aPTT, the target intensity of warfarin anticoagulation may have been achieved. The DTI infusion can be held for a period of time to allow sufficient loss of effects. To simplify the process, the infusion may be held over the night, and an INR with an aPTT drawn at a pre-selected time for assessment in the morning to determine if the infusion needs to be restarted, or discontinued if the INR is within target. The INR can be used to assess the degree of warfarin anticoagulation, and the aPTT to determine if any residual DTI effects continue to be present. Chromogenic factor II or Xa have also been used as a means to monitor warfarin response in settings where additional factor are in-

Table 12-3. CD

Transitioning from a DTI to Warfarin

1. Draw a baseline INR with an aPTT on DTI therapy alone.
2. Initiate warfarin and identify a desired 1.5–2 point increase in the INR, or a pre-selected INR, that considers the DTI-induced INR prolongation (with minimal change in the aPTT).
3. Once the desired number of overlap days and desired platelet recovery has occurred and the desired INR target is reached, hold the DTI for 4–8 hours and recheck the INR and aPTT. If the INR is between 2–3 with an aPTT close to baseline (accounting for warfarin related elevation), then the DTI can be discontinued. It may take longer for the effects of a DTI to diminish if a very low infusion rate with aPTT values in the target range.
4. Another option may be the use of chromogenic factor Xa or factor II to assess if an adequate anticoagulation response with warfarin has occured.[59-60]

Clinical Pearl

The DTI can independently elevate the INR value by interfering with the assay in the laboratory. Absent of warfarin, this should not be interpreted as an elevated degree of anticoagulation. The degree of effect on the INR may correlate with the concentration of the DTI present, which may be represented by the intensity of rise in the aPTT.

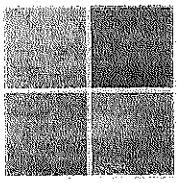
fluencing INR values are creating difficulties in determining the degree of warfarin anticoagulation.[59-60]

Reversal

Currently, there is no easy means to expedite reversal of a DTI. The use of activated recombinant factor VIIa has been suggested, but observations have been mixed on its effectiveness.[61] In addition are concerns of increased risk of thromboembolism with it use.[62] Hemodialysis and plasmapheresis can enhance the removal of both lepirudin and bivalirudin. The extent of removal for lepirudin during hemodialysis may depend on charge on the membrane surface of the dialyzer, with greater removal observed when negatively charged membranes are used.[27] The removal of bivalirudin may depend on the duration of dialysis, type of circuit and pore size of the membrane, and, to a limited extent, the electrostatic charge or the membrane.[6,63] In general, argatroban does not appear to be removed to any significant extent during hemodialysis.[33,39]

Conclusion

The DTIs represent a potent class of anticoagulants that can independently inhibit the functions of thrombin. Dosing can vary considerably depending on the indication for use, agent selected and clinical presentation of the patient. Then unique effects on coagulation related assays should be understood and incorporated into management plans. Careful consideration and understanding of these concepts are critical to optimizing the use of DTIs, which frequently occurs during acute, clinically concerning thrombosis related situations.



Patient Case

JM is a 67-yo, 85-kg, 5'6" female with hypertension, CHF, and chromic kidney disease (CKD stage III) who was admitted with chest pain and shortness of breath. The EKG was normal, however, there is a suspicion of a urinary tract infection. She was started on a heparin infusion for suspicion of a pulmonary embolism. Two days later the CT scan showed no evidence of a pulmonary embolism, and ultrasound of her legs showed no evidence of thrombus. She also was noted to have exacerbation of her CHF (ejection fraction 25%) and was continued on her heparin infusion for prophylaxis while being treated for the UTI with ceftriaxone. On hospital day 7, she was noted to have a platelet count decline to 75 from her baseline value or 289 on admission. The aPTT prior to starting heparin was 28 seconds.

Question 1: What alterations in the anticoagulation regimen and management plan would you consider?

Answer: The timing of heparin exposure fits the typical onset pattern for HIT along with a 50% drop in platelet count where a clear association with a separate primary cause is not present. Since the suspicion of HIT is not low, changing from heparin to a direct thrombin inhibitor may be considered along with a request for a heparin antibody test. Because the patient has renal insufficiency, argatroban may be the DTI to select. No acute thrombosis is present, so their may be time to initiate therapy at a lower infusion rate to avoid increased risk for bleeding associated with renal insufficiency, and the presence of heart failure with a low ejection fraction potentially reducing elimination.

An initial dose of 1 mcg/kg/min is chosen (approximated to 5 mg/h), with an aPTT requested 4 hours after starting the infusion. A target range of approximately 1.6–2.2 time control, or approximately 45 to 60 seconds was set since no thrombus was present. The aPTT at 4 hours is 59 seconds (INR 3.5). The infusion is continued at the current rate. Another aPTT 6 hours later with a.m. labs is 89 seconds with an INR of 4.5. The infusion is held and fresh frozen plasma (FFP) plus vitamin K 5 mg PO is ordered. The test for HIT antibody was reported as positive, with an optical density of 1.4 (negative cut-off < 0.4).

Question 2: Is discontinuing the Argatroban and administering FFP and Vitamin K clearly indicated?

Answer: Time to steady state is prolonged when clearance is reduced. The 59-second aPTT value at 4 hours, which could be steady state in healthy subjects, may not represent steady state in this patient and might continue to rise. As the aPTT value increased, so did the INR, suggesting an argatroban effect. The INR elevation did not represent a true state of excessive anticoagulation, so the request for vitamin K and FFP was likely not necessary. Holding the DTI for a prolonged period of time may also leave the patient with a very hypercoagulable condition unprotected against thrombosis formation, especially if the platelets have not recovered.

The argatroban is restarted, and, by day three, the argatroban infusion had been adjusted to 3 mg/h (approximately 0.6 mcg/kg/min) with an aPTT of 55 seconds (and INR 3.3), with a platelet count increased to 120 K/mm^3. Warfarin was requested for prophylaxis against HIT related thrombosis for 4 weeks. The initial dose was 10 mg PO times one.

Question 3: Is this an appropriate starting dose of warfarin in an HIT patient?

Answer: Overaggressive warfarin therapy in the setting of HIT is discouraged because of the risk for venous limb gangrene associated with overshooting warfarin related anticoagulation early in therapy. A more conservative regimen (5 mg or less) should be considered.

Question 4: When can a direct thrombin inhibitor be safely discontinued when transitioning to warfarin?

Answer: A measured INR around 5.0 while the aPTT is still within range may reflect a 1.5 to 2 point rise in the INR and a value of around 2.0 off the DTI. At this point, the infusion can be stopped as long as the platelet count has sufficiently recovered (at least to 100,000) with an INR and aPTT checked to verify adequate anticoagulation from warfarin alone. The low argatroban infusion rate may suggest a reduced clearance and that a longer hold (8–12 hours) may be necessary for the DTI effects to dissipate.

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