Clinical Use of Desirudin, a New Subcutaneously Administered Direct Thrombin Inhibitor

Introduction

Thrombin is a serine protease that plays a pivotal role in the coagulation process. It is produced via stepwise activation of proenzymes following vascular injury.1 Once formed, thrombin converts soluble fibrinogen to insoluble fibrin. It also stimulates platelets and enhances production of additional thrombin, facilitating blood clot stabilization.1 Higher thrombin concentrations are associated with denser, more rigid clots.1

Indirect anticoagulants, such as unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH), are used widely to prevent thrombosis in various patient populations.3-4 Heparins have several clinical limitations, however, including the inability to neutralize fibrin-bound thrombin; an unpredictable dose–response relationship; and the potential to induce immunomediated platelet activation, which can lead to heparin–induced thrombocytopaenia (HIT).1,4-6

Direct thrombin inhibitors (DTIs), considered “direct anticoagulants,” have intrinsic activity, offering several advantages over heparins: They do not require plasma cofactors (eg, antithrombin) to exert their effect; they inhibit both free and fibrin-bound thrombin; their use is not associated with HIT; and because they have little interaction with plasma proteins, their anticoagulant effects are more predictable than those of heparin.4,5 Four DTIs are approved for use as anticoagulants in the United States: desirudin (Iprivask®, Canyon), lepirudin (Refudan®, Bayer HealthCare), bivalirudin (Angiomax®, The Medicines Company), and argatroban (Argatroban, GlaxoSmithKline). They each have different indications and unique pharmacologic properties.4,5 Table 1 shows an overview of these 4 clinically distinct DTIs.4,5,6 Desirudin is anticipated to be available on the US market in late 2009. It is indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism in patients undergoing elective hip replacement surgery.20 Desirudin is the only DTI approved for subcutaneous administration.7-10 Desirudin may provide benefits related to dosing, administration, therapeutic monitoring, costs, and transition to oral anticoagulant therapy.

Clinical studies have shown that desirudin is significantly more effective than UFH and LMWH for preventing thromboembolic events in patients undergoing hip replacement surgery, with equal safety.11-12 Desirudin also has been studied in acute coronary syndromes13,14 and is currently under investigation for use in several other patient populations, including prophylaxis and treatment of thrombosis in patients who have or are at risk for HIT (subcutaneous administration), and for patients undergoing percutaneous intervention (PCI; administration of single IV bolus dose).

Pharmacology

DTIs differ in their potency, pharmacokinetic properties, monitoring requirements, and routes of administration.7-10 They often are classified according to potency or thrombin-binding affinity. Univalent DTIs bind only to the active (catalytic) site of thrombin, whereas bivalent DTIs interact with the fibrinogen-binding site (exo-site) I as well as the active thrombin site.1 Desirudin and lepirudin are high-affinity, bivalent DTIs that are recombinant analogs of hirudin, a peptide originally isolated from the salivary glands of medicinal leeches.4 Bivalirudin, also a bivalent DTI, is a synthetic analog of hirudin.4 However, bivalirudin differs from desirudin and lepirudin in 2 important ways. First, bivalirudin has a binding affinity for thrombin that is approximately 100,000 times less than the recombinant analogs; second, bivalirudin is cleaved by thrombin to inactive metabolites, resulting in an antithrombotic effect that is much more transient.1 Argatroban, a univalent DTI with the lowest relative affinity, also dissociates from thrombin after binding, leaving active thrombin available to facilitate hemostasis.1,4 Differences in thrombin-binding affinity may be associated with differences in efficacy among DTIs.10,11 A recent study in a porcine angioplasty model correlated higher thrombin-binding affinity with more potent antithrombotic effects. This suggests that DTIs with high thrombin-binding affinity (eg, desirudin) may be more efficacious than DTIs with much lower binding affinity (eg, argatroban, bivalirudin).17 This hypothesis is currently being investigated in clinical trials comparing desirudin with argatroban in HIT/heparin–induced thrombocytopenia with thrombosis syndrome (HITTS) and bivalirudin in PCI. These studies are the first prospective clinical trials investigating the safety and efficacy of parenteral DTIs as anticoagulants.

Dosage and Administration

Desirudin is the only DTI approved in the United States as a fixed-dose, subcutaneous formulation.7-10 The ability to administer desirudin subcutaneously gives practitioners the flexibility of prescribing the drug on an inpatient or outpatient basis. Other subcutaneously administered anticoagulants (eg, LMWHs) are commonly used for the treatment of venous thromboembolism (VTE) in the outpatient setting. This practice has been strongly associated with shorter hospitalizations, lower treatment costs, and similar outcomes when compared with inpatient management of VTE.18 Additionally, desirudin does not require weight-based dose calculations or continuous infusion as do heparins and the other DTIs.7-10 Medications that are administered via continuous infusion or require weight-based dosing are associated with increased potential for medication errors and adverse events.19,20 Studies show that patients given weight–based therapeutic anticoagulation are frequently dosed without being weighed, or the doses are based on incorrect weight estimations, resulting in dosing errors and increased hemorrhagic complications.19 As a result, subcutaneously administered, fixed–dose desirudin may allow for greater ease of use, flexibility, cost savings, and safety compared with other DTIs.

In patients undergoing orthopedic surgery, the recommended dose of desirudin is 15 mg given every 12 hours for up to 12 days. The initial dose of desirudin should be administered 5 to 15 minutes prior to surgery but after any regional block anesthesia. Prescribing information for desirudin currently recommends reduced doses for patients with moderate to severe renal impairment;21 however, recent data suggest that desirudin may be used without dose adjustments in patients with moderate impairment.21

IV administration of desirudin has been used in patients with cardiovascular disease.13,14 Doses of argatroban and bivalirudin—the DTIs currently indicated for use during PCI procedures—are calculated based on patient weight and administered via IV infusion. Subsequent doses of these agents may require adjustment according to targeted, activated clotting times.4,22 Desirudin currently is being investigated in the PCI setting as a single, fixed–dose IV bolus anticoagulant.

Monitoring

There are numerous clotting tests used to monitor the activity of the various anticoagulants. Because several reagents are available for use with these tests, results may vary and reproducibility of results is uncertain.6 Unlike heparin and the other DTIs, desirudin, as currently indicated, does not require routine monitoring unless increased risk for hemorrhage or renal impairment is present.10 However, if the clinician desires, desirudin can be monitored easily via activated partial thromboplastin time (aPTT). In most dosing situations, there is a linear correlation of desirudin with aPTT.22 The anticoagulant effects of desirudin will be monitored using both aPTT and activated clotting time in a clinical investigation of the comparative efficacy and safety of desirudin, bivalirudin, and UFH in the setting of PCI.23

Transition to Oral Therapy

The overall coagulation status of patients on DTIs should be monitored closely during transition to oral therapy.24 DTIs are known to have variable, dose–dependent effects on international normalized ratio (INR) values.4 Argatroban has the greatest impact on INR, which can complicate the transition to oral anticoagulant therapy during concurrent treatment.4,25 whereas desirudin and lepirudin have the least effect on INR.26,27 Transitioning to oral therapy may be less complicated with desirudin given its minimal effect on INR and its ability to be administered subcutaneously.22,24

Safety and Tolerability

In early clinical trials of desirudin, patients experienced unexpectedly high rates of bleeding compared with heparin.25,26 The daily doses of desirudin used in these clinical trials were approximately 13 times higher than the currently approved

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dose of desirudin, \(^{30,31,34}\) In recent clinical trials of DVT prophylaxis, safety and tolerability with the currently approved desirudin dose and formulation was similar to UFH and LMWH (enoxaparin). \(^{32}\) Further, in the study comparing desirudin to enoxaparin, the rate of serious bleeding in the desirudin group was nearly identical to the rate in the enoxaparin group (1.9% vs 2.0%, respectively), despite desirudin being administered within 30 minutes before surgery, whereas enoxaparin was given the evening before surgery. \(^{21}\)

Antibody formation following the administration of recombinant hirudins has been reported. Although a majority of the data available focus on lepirudin, antibody formation with desirudin also has been reported. \(^{6,27}\) Additionally, cross-reactivity with bivalirudin has been observed in approximately 40% of patients with hirudin-induced antibodies. Fatal anaphylactic reactions following administration of hirudins are rare. \(^{5}\)

Conclusions

Desirudin is the only DTI indicated for the prevention of DVT in patients undergoing total hip replacement surgery, and the only DTI approved for fixed-dose, subcutaneous administration. Given its desirable mechanistic and pharmacokinetic properties, desirudin may be a useful alternative to heparin anticoagulants and currently available DTIs. The use and indications of this potent anticoagulant are likely to expand to broader patient populations as results from ongoing studies in patients with HIT/HTTs and those undergoing PCI are reported.

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References


Table. Comparison of Direct Thrombin Inhibitors Available for Use in the United States

<table>
<thead>
<tr>
<th>Indication</th>
<th>Desirudin (Iprovask)(^{30,31})</th>
<th>Lepirudin (Refludan)(^{4})</th>
<th>Bivalirudin (Angiomax)(^{5})</th>
<th>Argatroban (Angatroban)(^{1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>THROMBIN AFFINITY*</td>
<td>Highest</td>
<td>Highest</td>
<td>Intermediate</td>
<td>Lowest</td>
</tr>
<tr>
<td>INDICATION</td>
<td>Anticoagulant for prophylaxis of DVT, which may lead to PE, in patients undergoing elective hip replacement surgery</td>
<td>Anticoagulant in patients with HIT and associated thromboembolic disease to prevent thromboembolic complications</td>
<td>Anticoagulant in patients with unstable angina undergoing PCI</td>
<td>Anticoagulant for prophylaxis or treatment of thrombosis in patients with HIT</td>
</tr>
<tr>
<td>DOSING AND ADMINISTRATION</td>
<td>- SC injection 5-15 min prior to surgery and every 12 h thereafter</td>
<td>- IV bolus followed by infusion</td>
<td>- IV bolus followed by infusion</td>
<td>- IV infusion</td>
</tr>
<tr>
<td></td>
<td>- Fixed dose</td>
<td>- Dose based on body weight and infusion rate</td>
<td>- Dose based on aPTT monitoring</td>
<td>- Dose adjustments required based on aPTT monitoring in HIT or ACT monitoring in PCI</td>
</tr>
<tr>
<td></td>
<td>- Dose adjustment in renal impairment</td>
<td>- Dose adjustment based on aPTT monitoring</td>
<td>- Intended for use with concomitant aspirin</td>
<td>- IV bolus followed by infusion in PCI</td>
</tr>
<tr>
<td></td>
<td>- IV bolus plus infusion in clinical trials of the medical management of ACS or PTCA</td>
<td>- Dose adjustment in renal impairment</td>
<td>- Dose adjustment based on ACT monitoring</td>
<td>- Dose adjustment in hepatic impairment</td>
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<td></td>
<td>- IV bolus only ongoing study in patients undergoing PCI</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>MONITORING</td>
<td>- Not required for most patients</td>
<td>- ACT monitoring 5 min after bolus</td>
<td>- ACT monitoring 5 min after bolus</td>
<td>- ACT monitoring in HIT/HTTS</td>
</tr>
<tr>
<td></td>
<td>- aPTT monitoring for patients at increased risk for hemorrhage and patients with renal impairment</td>
<td>- Additional monitoring required with renal impairment</td>
<td>- aPTT monitoring 2 h after initiation and dose changes</td>
<td>- aPTT monitoring during PCI</td>
</tr>
<tr>
<td></td>
<td>- aPTT ratio prior to use</td>
<td>- ACT monitoring during PCI</td>
<td>- Dose adjustment recommended in patients with hepatic impairment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- aPTT ratio 4 h following administration and once daily</td>
<td></td>
<td></td>
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<tr>
<td>HALF-LIFE</td>
<td>SC = 120 min</td>
<td>IV = 60 min</td>
<td>&gt;80 min</td>
<td>&gt;25 min</td>
</tr>
</tbody>
</table>

ACS, acute coronary syndrome; ACT, activated clotting time; aPTT, activated partial thromboplastin time; DVT, deep vein thrombosis; HIT, heparin-induced thrombocytopenia; HITTS, heparin-induced thrombocytopenia with thrombosis syndrome; IV, intravenous; PCI, percutaneous coronary intervention; PE, pulmonary embolism; PTCA, percutaneous transluminal coronary angioplasty; SC, subcutaneous

* Thrombin affinity based on Ki values reviewed by Warkentin.\(^{5}\)