Hirudin was used for the first parenteral anticoagulation in humans in 1909 and as the anticoagulant for the first hemodialysis in humans. Soon after, heparin became available and has since become the most widely used drug for parenteral anticoagulation. Heparin, however, can induce a life-threatening adverse immune reaction, heparin-induced thrombocytopenia (HIT), which up to 3% of patients receiving unfractionated heparin (UFH) for >5 days will develop.

HIT typically manifests 5 to 10 days after the start of heparin therapy. HIT antibodies bind to heparin platelet factor 4 (PF4) complexes, thereby activating platelets, generating platelet microparticles, and altering endothelial cells, leading to enhanced thrombin generation and paradoxical development of new thrombi.

Two prospective studies led to the first approval of a recombinant hirudin (r-hirudin), lepirudin, as an alternative for further parenteral anticoagulation of HIT patients in the European Union and United States. This review provides an overview of pharmacology and relevant clinical data of lepirudin with an emphasis on HIT and unstable angina. An overview of usage of lepirudin in acute coronary syndromes is given, as well as a summary of rare indications for lepirudin, such as extracorporeal circulation, for which comprehensive data are lacking. (Circulation. 2001;103:1479-1484.)

Key Words: recombinant hirudin ■ platelets ■ thrombosis ■ cardiovascular diseases ■ heparin

In healthy subjects, plasma pharmacokinetics follow a 2-compartment model, with a terminal plasma elimination half-life ($t_{1/2}$) of 0.8 to 1.7 hours after injection of bolus lepirudin doses of 0.01 to 0.5 mg/kg IV and 1.1 to 2.0 hours for continuous intravenous infusions over 6 hours. With subcutaneous administration, bioavailability is nearly 100%. After injection of 0.75 mg/kg SC, a peak lepirudin concentration of $\approx 0.7 \mu g/mL$ occurs in 3 to 4 hours.

Renal clearance and degradation account for $\approx 90\%$ of the systemic clearance. The $t_{1/2}$ of lepirudin lengthens with deterioration of renal function up to 150 hours.

Clinical Studies in HIT

In 2 prospective, multicenter, historically controlled trials, Heparin-Associated Thrombocytopenia (HAT)-1 ($n = 82$) and HAT-2 ($n = 112$) patients with clinical symptoms of HIT (decreased platelet count $>50\%$ and/or new thromboembolic complication) and laboratory confirmation of HIT antibodies were enrolled. Lepirudin allowed rapid normalization of low platelet counts or maintained normal platelet counts in 88.7% and 92.6% of patients, respectively, and led to stable therapeutic prolongation of activated partial thromboplastin time (aPTT) in 77.2% and 72.3% of patients over a mean treatment duration of 14.4 and 15.5 days. Both studies had similar mortality rates (7.3% and 9.8%); however, limb amputations (3.7% and 8.9%) and new thromboembolic complications (9.8% and 17.9%) differed. All fatalities were judged to be due to the underlying disease rather than to use of lepirudin.

Laboratory confirmation of the clinical diagnosis of HIT led to a delay in the start of treatment with lepirudin. Even though the pretreatment periods accounted for only 8.5% (2.6 days, HAT-1) and 6% (1.9 days, HAT-2) of the duration of each study, more than one third of all new thromboembolic

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complications and limb amputations occurred during this time period.

When these studies were conducted, a placebo-control study design was considered unethical, and no other active treatment was approved for further anticoagulation in HIT; therefore, results of lepirudin treatment were compared with those of a historical control group (n = 120). The incidence of the combined end point (new thromboembolic complications, limb amputation, death) at day 35 was 52.1% in the historical control group, 28.4% in HAT-1 (P = 0.014; adjusted risk ratio, 0.508; 95% CI, 0.290 to 0.892), and 31.9% in HAT-2 (P = 0.15; adjusted risk ratio, 0.709; 95% CI, 0.44 to 1.14). It must be taken into consideration, however, that the use of a historical control population is a major limitation when these treatment effects are estimated.

In both studies, there were more bleeding events in the lepirudin-treated group compared with historical control subjects, primarily in perioperative settings and at sites of catheter insertion (39.1% [HAT-1], 44.6% [HAT-2], and 27.2% [control group]). However, there was no significant difference in the frequency of bleedings requiring transfusion (9.9% [HAT-1], 12.9% [HAT-2], and 9.1% [control group]). Other treatment options in HIT are summarized elsewhere.21,22

Clinical Use of Lepirudin

### Dosage and Monitoring

An overview of the lepirudin dose regimens is given in Table 1.23-29

Generally, treatment with lepirudin can be monitored with the aPTT, which should be determined before treatment, 4 hours after the start of intravenous lepirudin treatment, 4 hours after every dosage change, and then at least once daily. In case of underdosage, the infusion rate should be increased by 20%; in overdosage, the infusion should be stopped for 2 hours after every dosage change, and then at least once daily. If the aPTT ratio is <1.5, or may be treated with an infusion starting at 0.005 mg·kg⁻¹·h⁻¹ IV. When a switch is made to oral anticoagulation, the lepirudin dose may be lowered to reach an aPTT ratio of ≈1.5 and discontinued when the international normalized ratio exceeds 2.0.13,14,30

<table>
<thead>
<tr>
<th>TABLE 1. Dosing Schedules Tested in Lepirudin Studies</th>
<th>Bolus*</th>
<th>Intravenous Infusion*</th>
<th>Target aPTT Ratio†</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIT and thrombosis15,14§§</td>
<td>0.4 mg/kg IV</td>
<td>0.15 mg·kg⁻¹·h⁻¹</td>
<td>1.5–2.5</td>
</tr>
<tr>
<td>HIT with thrombosis and concomitant thrombolysis15,14§§</td>
<td>0.2 mg/kg IV</td>
<td>0.1 mg·kg⁻¹·h⁻¹</td>
<td>1.5–2.5</td>
</tr>
<tr>
<td>HIT with isolated thrombocytopenia13,14§§</td>
<td>0.1 mg·kg⁻¹·h⁻¹</td>
<td>1.5–2.0</td>
<td></td>
</tr>
<tr>
<td>Thrombolysis prophylaxis in patients with history of HIT13,14§§</td>
<td>0.1 mg·kg⁻¹·h⁻¹</td>
<td>1.5–2.0</td>
<td></td>
</tr>
<tr>
<td>Renal dialysis every alternate day20,23#</td>
<td>0.08–0.1 mg/kg intravenous predialysis</td>
<td>0.005 mg·kg⁻¹·h⁻¹</td>
<td>1.5–2.5</td>
</tr>
<tr>
<td>Renal dialysis or CVVH in intensive care unit patients¶</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPB surgery24§</td>
<td>0.25 mg/kg IV</td>
<td>0.15 mg·kg⁻¹·h⁻¹</td>
<td>aPTT 60–100 s</td>
</tr>
<tr>
<td>Unstable angina25††</td>
<td>0.4 mg/kg IV</td>
<td>0.12 mg·kg⁻¹·h⁻¹ for 24 h or 0.24 mg·kg⁻¹·h⁻¹ for 24 h followed by 0.04 mg·kg⁻¹·h⁻¹ for 24 h</td>
<td></td>
</tr>
<tr>
<td>PTCA26‡‡</td>
<td>0.3 or 0.5 mg/kg IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute MI27††</td>
<td>0.2 mg/kg IV</td>
<td>0.5 mg·kg⁻¹·h⁻¹ BID SC</td>
<td>1.5–2.0</td>
</tr>
</tbody>
</table>

CVH indicates chronic veno-venous hemofiltration; CPB, cardiopulmonary bypass; and HLM, heart-lung machine. Few data are available for dose recommendations in children; because of a lack of data, lepirudin cannot be recommended during pregnancy and lactation. During concomitant treatment with ASA, GP IIb/IIIa inhibitors, and fibrinolysis and in patients with platelet counts <100 000 μL, bleeding risk is increased and dosage may have to be reduced. In patients with renal impairment, dosage must be reduced to avoid overdosage.

††From prospective multicenter trials (historical control groups).
‡‡From prospective randomized, double-blind trials.
§From prospective randomized, open trial.
#From crossover study, dose-escalation trial.
¶From case observations.
†If Actin FS or Neothromtin reagents are used in Europe, different ranges may apply (eg, 1.5–3.0).
††From prospective multicenter trials (historical control groups).
‡‡From prospective randomized, double-blind trials.
§From prospective randomized, open trial.
#From crossover study, dose-escalation trial.
¶From case observations.
††From prospective, randomized, double-blind trials.
‡‡From prospective, randomized, open trial.

Desirudin has been shown to be effective in a dosage of 15 mg SC BID following orthopedic hip replacement surgery.29††
Potential problems with the use of the aPTT are its considerable variability between patients and a nonlinear correlation with lepirudin plasma levels. Especially at higher concentrations, the ecarin clotting time (ECT) shows a more linear correlation to lepirudin plasma levels. Prospective comparative studies between the 2 monitoring methods are lacking.

The activated clotting time was found to correlate poorly with hirudin plasma levels (≥0.07 μg/mL) during cardiopulmonary bypass.

Hemorrhage

In all reported clinical studies, minor bleedings were more frequent in lepirudin-treated patients than in control patients. Incidences of bleeding complications were strongly related to duration of treatment, underlying disease, and comedication, particularly thrombolsys. For different syndromes treated with the same lepirudin dose (0.4 mg/kg IV bolus followed by 0.15 mg·kg⁻¹·h⁻¹ IV infusion), bleeding risk was therefore different. Major hemorrhage occurred in HIT in ~12% of patients treated with lepirudin (historical control, ~9%), in myocardial infarction (MI) plus acetyl salicylic acid (ASA) plus thrombolysis in ~8% (heparin ~2%), and in unstable angina (UA) plus ASA in 1.2% of patients (heparin, 0.7%).

Neutralization of r-Hirudin

No specific antidote is available to neutralize r-hirudin. Small studies in human volunteers demonstrated a reversing effect of Desmopressin. Hirudin-induced bleeding diathesis was reversed by prothrombin complex, hemofiltration, hollow-fiber filters (cutoff, 50,000 Da), and high- and low-flux polysulfondialysers.

Drug Interactions

Lepirudin and desirudin have been assessed together with ASA, tissue plasminogen activator, and streptokinase (SK) in patients with acute coronary syndromes. Although several thrombolsys studies had to be stopped prematurely because of an unacceptably high rate of cerebral hemorrhag with higher hirudin doses (0.4 mg/kg bolus plus 0.15 mg·kg⁻¹·h⁻¹ IV infusion), or 0.6 mg/kg bolus plus 0.2 mg·kg⁻¹·h⁻¹ IV infusion), the Global Utilization of Streptokinase and TPA for Ocular Arteries (GUSTO II) study suggested clinical benefit of hirudin for the SK-treated patients, and the Hirulog versus heparin in patients receiving streptokinase (HERO-I) trial showed higher patency with bivalirudin and SK compared with heparin and SK.

ASA shows an additive effect on bleeding time in individuals treated with hirudin. It is unknown how hirudin interacts in vivo with GP IIb/IIIa inhibitors, ADP receptor antagonists, UFH, or low-molecular-weight heparin. In vitro experiments indicate that GP IIb/IIIa inhibitors also inhibit thrombin generation on the platelet surface, suggesting that combined use could increase bleeding risk.

Induction of Antibodies

Lepirudin has immunogenic properties. Of 198 HIT patients treated for ≥5 days with lepirudin, 45% developed anti-hirudin antibodies. In 2% to 3% of them, the antibodies seemed to have an enhancing effect, because hirudin dose had to be decreased by >60% to maintain the aPTT within the target range, probably by a decreased renal clearance of the lepirudin-immunoglobulin complexes.

Lepirudin in Coronary Artery Disease

Hirudin but not heparin significantly reduced platelet deposition and eliminated mural thrombosis in a deep carotid injury animal model. In humans, hirudins have been shown to be effective in acute coronary syndromes without ST elevation (UA), PTCA, and MI. The therapeutic window of hirudins, however, is very narrow.

Acute Coronary Syndromes Without ST Elevation

Lepirudin has been evaluated in patients with UA as an adjunct to ASA in 3 trials: the Antiplatelet Trials (APT) pilot study, Organization to Assess Strategies for Ischemic Syndromes (OASIS-I), and OASIS-II. In OASIS-I, patients with acute chest pain suspected to be due to acute coronary syndrome without ST elevation were randomized to receive 1 of 2 lepirudin doses or UFH for 72 hours (Table 2). At 7 days, fewer subjects in the group treated with lepirudin (0.4 mg/kg bolus plus 0.15 mg·kg⁻¹·h⁻¹ IV infusion) with UFH. The rate of death and MI at 30 days was significantly lower in the lepirudin group (95% CI, 0.21 to 1.02; P=0.047). In the double-blind OASIS-II trial, the primary end point of cardiovascular death or new MI at day 7 showed a trend in favor of lepirudin-treated patients (Table 2). Fewer interventions (CABG, PTCA, intra-aortic balloon pump, thrombolytic therapy) were needed in lepirudin-treated patients (Table 2).

A meta-analysis of the combined data of the 2 OASIS studies at 7 days showed that compared with UFH, lepirudin provided a 19% RR reduction (95% CI, 2 to 33; P=0.039) in cardiovascular death or MI; a 20% RR reduction (95% CI, 6 to 32; P=0.005) in cardiovascular death, MI, or refractory angina; a 17% RR reduction (95% CI, 5 to 28; P=0.009) in need for interventions during the first 7 days; and a 14% RR reduction (95% CI, 1 to 26; P=0.04) in death or MI at 35 days. In OASIS-II, there was an increase of 0.5% in major bleedings in lepirudin-treated patients (0.7% versus 1.2%; RR, 1.73; 95% CI, 1.13 to 2.63; P=0.01) but no difference in life-threatening bleedings (0.4% versus 0.4%).

Similar trends were observed in the GUSTO IIb trial comparing desirudin (0.1 mg/kg bolus plus 0.1 mg·kg⁻¹·h⁻¹ IV infusion) with UFH. The rate of death and MI at 30 days was lower in the desirudin group (9.8% versus 8.9%; OR, 0.89; 95% CI, 0.79 to 1.00; P=0.058) without reaching statistical significance, whereas the risk of moderate bleeding was slightly higher (8.8% versus 7.7%; P=0.03).

Acute MI

Lepirudin has been assessed in patients with acute MI as an adjunct to thrombolytic therapy with alteplase or SK and ASA in 5 studies (Hirudin for the Improvement of Thrombolysis [HIT]-I, HIT-II, HIT-III, HIT-IV, and HIT-SK). In essence, lepirudin, as an adjunct to thrombolytic therapy and ASA, is at least as effective as UFH with respect to early and sustained patency rates and clinical outcome.
TABLE 2. Outcomes of OASIS I and OASIS II in Patients With Acute Coronary Syndromes Without ST Elevation\textsuperscript{28,50}

<table>
<thead>
<tr>
<th></th>
<th>Heparin, 5000 U bolus +15 U kg\textsuperscript{−1} h\textsuperscript{−1} IV for 72 h, n (%)</th>
<th>Lepirudin, 0.4 mg/kg bolus+0.15 mg kg\textsuperscript{−1} h\textsuperscript{−1} IV for 72 h*, n (%)</th>
<th>RR (95% CI)</th>
<th>Unadjusted P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death/MI at 7 d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OASIS I</td>
<td>18/371 (4.9)</td>
<td>14/538 (2.6)</td>
<td>0.54 (0.27–1.06)</td>
<td>0.07</td>
</tr>
<tr>
<td>OASIS II</td>
<td>213/5058 (4.2)</td>
<td>182/5083 (3.6)</td>
<td>0.84 (0.69–1.02)</td>
<td>0.077</td>
</tr>
<tr>
<td>Total</td>
<td>231/5429 (4.3)</td>
<td>196/5621 (3.5)</td>
<td>0.81 (0.67–0.98)</td>
<td>0.039</td>
</tr>
<tr>
<td>Need for interventions (CABG, PTCA), intra-aortic balloon pump, thrombolytic therapy at 7 d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OASIS I</td>
<td>32/371 (8.6)</td>
<td>36/538 (6.7)</td>
<td>0.78 (0.49–1.23)</td>
<td>0.276</td>
</tr>
<tr>
<td>OASIS II</td>
<td>411/5058 (8.1)</td>
<td>349/5083 (6.8)</td>
<td>0.84 (0.74–0.97)</td>
<td>0.016</td>
</tr>
<tr>
<td>Total</td>
<td>433/5429 (8.2)</td>
<td>385/5621 (6.8)</td>
<td>0.83 (0.72–0.95)</td>
<td>0.009</td>
</tr>
<tr>
<td>Death/MI at 35 d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OASIS I</td>
<td>32/371 (8.6)</td>
<td>33/538 (6.1)</td>
<td>0.71 (0.44–1.14)</td>
<td>0.15</td>
</tr>
<tr>
<td>OASIS II</td>
<td>388/5058 (7.7)</td>
<td>345/5083 (6.8)</td>
<td>0.87 (0.75–1.01)</td>
<td>0.06</td>
</tr>
<tr>
<td>Total</td>
<td>420/5429 (7.7)</td>
<td>378/5621 (6.7)</td>
<td>0.86 (0.74–0.99)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*In OASIS I, 271 patients received a reduced dose of 0.2 mg/kg bolus plus 0.1 mg/kg IV.

However, the drug was associated with an unacceptably high risk of severe hemorrhages when used at the highest dosage (0.4 mg/kg plus 0.15 mg kg\textsuperscript{−1} h\textsuperscript{−1}). Similar data have been obtained with desirudin (0.6 mg/kg plus 0.2 mg kg\textsuperscript{−1} h\textsuperscript{−1}). The safety problem can be solved at the cost of reduced efficacy by use of a substantially reduced hirudin dosage. In the HIT-IV study (n=1208), a subcutaneous regimen of lepirudin (0.2 mg/kg plus 0.5 mg/kg SC BID for 5 to 7 days) was compared with UFH in conjunction with SK. The clinical outcome was similar in both groups with respect to bleeding events and efficacy end points; complete resolution of ST-segment elevation at 90 minutes was 28\% versus 22\% (P=0.05) and at 180 minutes was 52\% versus 48\% (P=0.18). Similarly, compared with UFH, desirudin at a reduced dose (0.1 mg/kg bolus followed by 0.1 mg kg\textsuperscript{−1} h\textsuperscript{−1}) showed equal effects as an adjunctive therapy to tissue plasminogen activator and SK in MI patients, with similar rates of major bleeding.\textsuperscript{55}

PTCA

A multicenter, open pilot trial\textsuperscript{56} comparing the effects of 2 lepirudin dose regimens with UFH in patients undergoing coronary angioplasty for UA (n=61; for doses, see Table 1) suggested a dose-dependent reduction in troponin T levels after the procedure. Desirudin (40 mg bolus plus 0.2 mg kg\textsuperscript{−1} h\textsuperscript{−1} for 24 hours, followed by 40 mcg SC BID) reduced early cardiac events in a prospective, randomized trial of 1141 patients undergoing PTCA but had no apparent benefit with longer-term follow-up.\textsuperscript{26}

Other Indications

Deep Vein Thrombosis

Desirudin (15 mg SC BID) has been shown to be more effective than low-molecular-weight heparin in preventing deep vein thrombosis in orthopedic hip replacement surgery.\textsuperscript{29} No conclusive data are available for lepirudin. At present, hirudins are much more expensive than low-molecular-weight heparins. However, no cost-effectiveness data assessing the overall cost are available. For treatment of deep vein thrombosis (other than in HIT patients), no recommendations can be made yet for lepirudin because of small numbers in the only randomized trial.\textsuperscript{57}

Dialysis

In a crossover study (n=11), lepirudin (0.15 mg/kg) and heparin (5000 to 10000 IU) were similarly effective with respect to urea, uric acid, and creatinine.\textsuperscript{25}

On the basis of a dose-escalation study, a bolus of 0.08 mg/kg lepirudin before regular hemodialysis is recommended.\textsuperscript{20} Nowak et al\textsuperscript{19} reported on a patient dialyzed with hirudin (r-hirudin HV1) with dosages of 0.16 and 0.145 mg/kg. In patients with HIT and acute renal failure, a reduced dosage is often sufficient for safe hemodialysis or hemofiltration (0.005 mg kg\textsuperscript{−1} h\textsuperscript{−1}; unpublished observation). Recovering diuresis, however, can lead to the need for drastically increased lepirudin doses.

CABG Surgery

In humans undergoing cardiac pulmonary bypass surgery with lepirudin, close monitoring by use of the ECT is essential. Pötzsch and Madlener\textsuperscript{24} developed an algorithm suggesting a pre–cardiac pulmonary bypass bolus of 0.25 mg/kg, with 0.2 mg/kg added to the priming solution. Plasma levels at the start of cardiac pulmonary bypass surgery should be \textgreater 2.5 μg/mL. During the surgery, 0.5 mg/min should be infused continuously and adjusted with the use of ECT measurements every 15 minutes. The infusion should be stopped 15 minutes before the end of cardiac pulmonary bypass surgery. Patients with impaired renal function may require hemofiltration to reduce lepirudin plasma levels.\textsuperscript{24} The use of lepirudin in cardiac pulmonary bypass surgery is currently restricted to patients with HIT.

Conclusions

Lepirudin has a definite role in the treatment of patients with HIT and desirudin in thrombosis prophylaxis. UA is a
potential new indication for the drug; however, r-hirudin should be compared with low-molecular-weight heparins for effectiveness and cost. There are many other indications in which lepirudin has shown feasibility, but insufficient data allow only limited conclusions.

The most important adverse effects of lepirudin treatment are hemorrhages and the induction of anti-hirudin antibodies. Definition of the optimal method of lepirudin monitoring and availability of an antidote for hirudin would probably increase drug safety. Anti-hirudin antibodies paradoxically enhance the pharmacological effect of lepirudin in a subset of patients but otherwise seem to be clinically irrelevant.

Other thrombin antagonists, such as argatroban or PEG-hirudin, are currently undergoing clinical trials and will probably add to the scope of clinical uses that this class of drugs has.

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