Safety Observations From the Pilot Phase of the Randomized r-Hirudin for Improvement of Thrombolysis (HIT-III) Study

A Study of the Arbeitsgemeinschaft Leitender Kardiologischer Krankenhausärzte (ALKK)

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Background Adjunctive therapy for thrombolysis in acute myocardial infarction consists of platelet inhibition with aspirin and thrombin inhibition with heparin. Thrombin inhibition may be improved by the use of hirudin as indicated by experimental and phase II clinical studies. The randomized, double-blind phase III r-Hirudin for Improvement of Thrombolysis study (HIT III) compared a recombinant hirudin (HBW 023) with heparin. The primary end point was the incidence of death or reinfarction.

Methods and Results Seven thousand patients with acute myocardial infarction and a duration of symptoms of less than 6 hours were to be randomized to receive intravenous heparin (70 IU/kg body wt bolus and 15 IU · kg⁻¹ · h⁻¹) or hirudin (0.4 mg/kg body wt bolus and 0.15 mg · kg⁻¹ · h⁻¹) infused over 48 to 72 hours and adjusted to an activated partial thromboplastin time of 2 to 3.5 times baseline values. In a pilot phase, 1000 patients receiving front-loaded alteplase for thrombolysis were to be recruited by 93 German centers. After enrollment of 302 patients, the trial was stopped after an increased rate of intracranial bleeding was observed in the hirudin group (5 of 148, 3.4%) compared with the heparin group (0 of 154). The overall stroke rate was 3.4% in the hirudin group and 1.3% in the heparin group. Other major bleeding occurred in five versus three patients and ventricular rupture occurred in three versus one patient in the hirudin and heparin groups, respectively. There were 19 in-hospital deaths, with 13 of them from the hirudin group.

Conclusions Although the number of patients was too small for a definite benefit-risk assessment, at the dosage tested, hirudin in combination with front-loaded alteplase and aspirin may be associated with an increased rate of intracranial hemorrhage. Our findings are consistent with the observations of the GUSTO-II and TIMI-9 trials, where higher doses of another recombinant hirudin were used. Therefore, the therapeutic range of hirudin as an adjunct to thrombolysis may be smaller than previously thought, and reappraisal of dose finding should be considered. (Circulation. 1994;90:1638-1642.)

Key Words • hirudin • thrombolysis • hemorrhage • clinical trials

Coronary artery reperfusion by thrombolysis in patients with acute myocardial infarction (AMI) has proved to be a major advance in cardiac medicine, leading to improvement in left ventricular ejection fraction1,2 and to a reduction in mortality.3,4 Nevertheless, current thrombolytic therapy is limited by the fact that despite adequate adjunctive heparin therapy, fewer than 60% of patients achieve optimal early reperfusion, and of reperfused vessels, 10% to 20% reocclude during the hospital stay.5 Both failure to achieve complete early reperfusion and coronary artery reocclusion are associated with increased morbidity and mortality.6,7 Ongoing thrombin formation during thrombolysis, even in the presence of intravenous heparin therapy, is a significant predisposing factor for reocclusion.8,9 Recently, a number of experimental studies investigating the direct thrombin inhibitor hirudin have shown promising results.10,11

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A complete list of the investigators is given in “Appendix.”
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with either rTPA or streptokinase from many international institutions. Due to an increased frequency of major bleeding events, the study was terminated prematurely after the inclusion of 302 patients. The preliminary results as of July 21, 1994, are presented in the following report.

**Methods**

The study was a prospective, randomized, double-blind multicenter trial in male and female patients with AMI and age above 18 years. The study protocol was approved by the Ethics Committee of the University of Göttingen and by the relevant institutional review boards of the participating centers. Patients with chest pain indicative of myocardial infarction with onset of symptoms within 6 hours were eligible if none of the established contraindications to thrombolysis or evidence of renal insufficiency was present. All patients gave informed consent.

**Treatment Protocol**

Patients fulfilling inclusion and exclusion criteria were randomized by the investigator telephoning a 24-hour service. The investigator was given the number of a treatment pack containing the trial medication for the patient.

All patients were to receive acetylsalicylic acid (ASA) with an initial dose of 250 mg PO. Then, each patient was given a bolus of either hirudin (0.4 mg/kg body wt) or heparin (70 IU/kg body wt). The yeast-derived recombinant [Leu1, Thr363]-desulfoteridin and matching placebo were manufactured and supplied as a lyophillate by Hoechst AG/Behringwerke AG. Unfractionated heparin and matching placebo were purchased from Braun Melsungen. Thrombolytic therapy with rTPA (Actilyse® [alteplase], purchased from Thaem GmbH) was given according to the regimen of Neuhaus et al: 15 mg rTPA was given as IV bolus followed by 50 mg over 30 minutes and another 35 mg over the next 60 minutes. As soon as the thrombolytic infusion had been started, the blinded infusion of hirudin (0.15 mg · kg body wt⁻¹ · h⁻¹) or heparin (15 IU · kg body wt⁻¹ · h⁻¹) was started. The IV infusion of the trial medication was continued for at least 48 hours but could be prolonged up to 72 hours in patients with ongoing symptoms of cardiac ischemia. It was recommended that all patients receive long-term ASA therapy at a daily dose of 100 to 500 mg PO. Upward dose adjustments of the anticoagulant infusion were performed in case the activated partial thromboplastin time (aPTT) was below 2.0-fold prolongation of the aPTT baseline value. In this case, the infusion rate was to be increased by 20%. In patients with aPTT values above 3.5-fold baseline, the infusion rate was to be reduced by 20%. As a safeguard against potential overdosing or underdosing, dosage adjustment in either direction was not to be done more than twice. However, over the first 24 hours, no dose adjustments for high aPTT values were recommended unless mandated by occurrence of bleeding. On April 18, 1994, a protocol amendment was implemented requesting another aPTT determination 4 hours after start of the trial medication. In all patients for whom the 4-hour aPTT was above 3.5-fold of baseline, therapy had to be interrupted for at least 2 hours to avoid early excessive anticoagulation.

**Data Collection**

Before the start of the trial medication, a 12-lead ECG was to be performed in each patient, and blood samples for baseline values were taken. Coagulation parameters and cardiac enzymes were to be determined again after 24 and 48 hours, at the end of infusions, and on discharge. Twelve-lead ECGs were performed 48 and 72 hours after the start of treatment and on discharge. In patients with stroke, confirmation of diagnosis by computed tomography, magnetic resonance imaging, or autopsy was requested wherever feasible. The survival status of the patients was to be determined on day 30 and after 1 year.

Particular emphasis was put on the documentation of adverse events. All deaths, strokes, life-threatening bleeding events, anaphylactic shocks, or other unexpected serious adverse events occurring from the time of randomization until day 16 or hospital discharge, if earlier, were to be reported immediately to the study coordinating center. After inclusion of every 100 patients, an extensive safety report was prepared listing all serious adverse events in a blinded fashion. The chairman of the Safety Committee had access to a randomization code, allowing grouping of patients according to “treatment group A” and “treatment group B” without further unblinding.

**Primary End Point**

The primary end point was a composite of the 30-day mortality and in-hospital reinfarction rates. Reinfarction occurring within 24 hours after the start of treatment was defined as recurrent severe ischemic pain lasting at least 15 minutes and associated with recurrent ST-segment elevation. Reinfarction after 24 hours was defined as recurrent ischemic symptoms lasting for more than 15 minutes and being associated with ECG and enzyme evidence of reinfarction.

**Secondary End Point**

As the secondary end point, the incidence of stroke (hemorrhagic or ischemic), of other major bleeding, and of cardiac morbidity was assessed.

**Statistical Analysis**

For the primary end point, a sample size of 7000 patients was calculated to show a 20% relative reduction in death or reinfarction from 9.1% to 7.8%. Approximately 1000 patients were to be included in the pilot phase of the trial. No interim analysis was planned, but regular updates were provided to the Safety Committee with respect to major bleeding and other serious adverse events. For the primary efficacy variable, the combined end point of 30-day mortality and the in-hospital incidence of nonfatal reinfarction, the Cochran-Mantel-Haenszel test was to be used. Primary end point data will be presented with the final results of the study. As no interim analysis was planned, the P values calculated are provided only as a descriptive measure of imbalance outside the framework of hypothesis testing and statistical significance.

**Results**

**Patients**

Patient recruitment started on March 9, 1991. On the recommendation of the Safety Committee, patient recruitment was terminated on June 29, 1994, after inclusion of 302 patients, due to an imbalance in the incidence of major bleeding events. This report focuses on the major safety variables as reported by the clinical sites for all patients and on additional information from 246 patients for whom data from case record forms were available as of July 21, 1994. The primary end point data as well as a more extensive presentation of secondary outcome parameters will be presented elsewhere.

**Baseline Characteristics**

The major baseline characteristics are depicted in Table 1. Groups were comparable with respect to age, sex, and weight as well as systolic blood pressure and heart rate. In the majority of patients, treatment was started within 3 hours after onset of symptoms. The patients included into this study were not at “low risk,”...
with 23% of patients >70 years old and 40% of patients with anterior AMI. However, the distribution of high-risk patients was similar in the two groups.

Mortality
During the in-hospital/observation period, 19 deaths were reported: 13 of 148 (8.8%) in the hirudin group and 6 of 154 (3.9%) in the heparin group ($P=0.1$; Table 2). Thirty-day follow-up was incomplete at the time of this report.

There were nine cardiac deaths (6.1%) in the hirudin group, three of which were due to cardiac rupture. Four additional deaths in the hirudin group were due to hemorrhagic stroke (2.7%). In the heparin group, five deaths were due to cardiac causes (3.2%), one of which was a cardiac rupture. One patient had a fatal ischemic stroke (0.6%).

Cerebrovascular Accidents
There were five strokes in the hirudin group, four of them hemorrhagic strokes confirmed by computed tomography or autopsy and one classified as hemorrhagic because of clinical symptoms. Four of these events were fatal (see above). In the heparin group, two ischemic strokes occurred, one of which was fatal. Thus, the overall stroke rate was 3.4% in the hirudin group and 1.3% in the heparin group ($P=0.27$). All hemorrhagic strokes occurred within 24 hours (5, 6, 6.5, 13, and 23 hours from treatment onset), whereas the ischemic strokes occurred on days 2 and 17.

Major Bleeding Other Than Stroke
There were eight other major bleeding events (Table 3), five of which occurred in the hirudin group (3.4%) and three in the heparin group (1.9%). In five patients of the hirudin group, spontaneous gastrointestinal bleeding occurred. In the heparin group, one genitourinary bleeding, one hematoma necessitating transfusion, and one major puncture site bleeding were observed.

aPTT
Baseline median aPTT values in patients with bleeding events were comparable to those without bleeding (Table 4). Determination of aPTT 24 hours after the start of therapy showed a considerably higher median aPTT value in seven patients with aPTT available who received hirudin and had a bleeding event compared with those who did not (106 versus 76 seconds). In the heparin group, aPTT values after 24 hours were available in three patients with bleeding events. Their median was not different from that in patients without bleeding (53 versus 58 seconds).

Table 2. Fatal Events During the In-Hospital/Observation Period

<table>
<thead>
<tr>
<th>Event</th>
<th>HIRUDIN Group (n=148)</th>
<th>HEPARIN Group (n=154)</th>
<th>Nominal P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac death, n</td>
<td>9 (6.1%)</td>
<td>5 (3.2%)</td>
<td>.28</td>
</tr>
<tr>
<td>Confirmed cardiac rupture</td>
<td>3 (2.0%)</td>
<td>1 (0.6%)</td>
<td></td>
</tr>
<tr>
<td>Other cardiac cause</td>
<td>6 (4.1%)</td>
<td>4 (2.6%)</td>
<td></td>
</tr>
<tr>
<td>Fatal stroke, n</td>
<td>4 (2.7%)</td>
<td>1 (0.6%)</td>
<td>.20</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>4 (2.7%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0</td>
<td>1 (0.6%)</td>
<td></td>
</tr>
<tr>
<td>Overall early mortality, n</td>
<td>13 (8.8%)</td>
<td>6 (3.9%)</td>
<td>.1</td>
</tr>
</tbody>
</table>

*All P values are two-tailed and based on Fisher’s exact test.

Discussion
The HIT-III trial is the third phase III study after TIMI-9 and GUSTO-II that compares heparin with hirudin as antithrombin adjuncts to thrombolysis in AMI. Although in HIT-III a different hirudin was used, the basic features of the three trials are quite similar; therefore, stopping both TIMI-9 and GUSTO-II for safety reasons 4 weeks after enrollment into HIT-III had begun caused major concern for safety for the HIT-III trial as well. Both the Safety Committee and the Steering Committee decided to continue enrollment because the bolus dose was substantially smaller (0.4 versus 0.6 mg/kg body wt) and the infusion rate was lower (0.15 versus 0.2 mg·kg⁻¹·h⁻¹) than in GUSTO-II and TIMI-9. As an additional safeguard, an amendment to the study protocol was made as detailed above, and the Safety Committee was prompted to reassess safety after inclusion of every 100 patients. Furthermore, the Safety Committee was immediately notified of all cases of stroke. This extremely close safety monitoring turned out to be adequate since after inclusion of 300 patients, recruitment was terminated because of an unexpectedly high rate of major bleeding.

Table 3. Nonfatal Stroke and Major Bleeding Events

<table>
<thead>
<tr>
<th>Event</th>
<th>HIRUDIN Group (n=148)</th>
<th>HEPARIN Group (n=154)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal stroke, n</td>
<td>1 (0.7%)</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>1 (0.7%)</td>
<td>0</td>
</tr>
<tr>
<td>Ischemic</td>
<td>0</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Major bleeding (other than stroke), n</td>
<td>5 (3.4%)</td>
<td>3 (1.9%)</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>5 (3.4%)</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td>Puncture site</td>
<td>0</td>
<td>1 (0.6%)</td>
</tr>
</tbody>
</table>
A high rate of intracerebral hemorrhage in the hirudin group. In the heparin group, an increased bleeding rate was not observed, which may be due to weight-adjusted dosing and further adjustment for aPTT values of 2.0 to 3.5 times baseline. From the relatively small total number of patients with major bleeding in this trial, the impact of aPTT as an indicator of risk cannot be assessed adequately; however, there was a trend to higher aPTT in patients who were treated with hirudin and had a major bleeding event (Table 4). At least for the prevention of intracranial hemorrhage, aPTT determinations would be of limited value, since three of these events were clinically manifest within 6 hours from treatment onset, and the other two occurred after 13 and 23 hours, respectively.

Even though the safety findings from HIT-III are not strictly conclusive on their own, the consistent observation of high rates of life-threatening bleeding in three independent trials with two hirudins and two different fibrinolytics raises important questions. Apart from issues regarding patient selection (age, comorbidity), the combination of hirudin and thrombolysis per se might increase the risk of bleeding via potentiating effects on fibrinolysis and/or hemostasis mechanisms. On the other hand, it may be simply a dosing problem that was not identified in phase II studies. Similar observed bleeding rates with significantly lower doses of hirudin in the HIT-III trial than in the GUSTO II and TIMI 9 trials point to a therapeutic range narrower than previously thought, at least in combination with thrombolitics. The definition of a hirudin regimen that is more efficacious than heparin and at least as safe might need reappraisal of the drug by another phase II trial.

Acknowledgment

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Appendix

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