Initial Experience With a Direct Antithrombin, Hirulog, in Unstable Angina
Anticoagulant, Antithrombotic, and Clinical Effects

Rosa-Maria Lidón, MD; Pierre Théroux, MD; Martin Juneau, MD; Burt Adelman, MD; John Maraganore, PhD

Background. Currently available antithrombotic therapy for unstable angina is unwieldy and occasionally ineffective. This study was designed to investigate the potential of Hirulog, a new synthetic specific antithrombin agent, for the management of this condition.

Methods and Results. A total of 55 patients in the acute phase of unstable angina received intravenous Hirulog according to one of two protocols. In an acute dose-escalating study, 0.02, 0.05, 0.1, 0.25, and 0.5 mg · kg⁻¹ · h⁻¹, each for 30 minutes, were infused in 15 patients. Prolongation of activated partial thromboplastin time (aPTT) (r=.95), fibrinopeptide A inhibition (r=.96), and Hirulog plasma levels (r=.91) correlated closely with the dose infused, with significant changes compared with baseline appearing at doses of 0.25 mg · kg⁻¹ · h⁻¹ and higher. The purposes of the second protocol were to determine whether the anticoagulant and antithrombotic effects of the drug were sustained during a 72-hour infusion and to assess whether such treatment prevented the complications of unstable angina.

Based on the initial study, we planned to give a dose of 0.25 mg · kg⁻¹ · h⁻¹ to each patient until 2 patients failed therapy, then successively higher doses until a 95% success rate was achieved or adverse effects intervened, increasing the dose after two failures had occurred at each level. Five patients received the 0.25-mg · kg⁻¹ · h⁻¹ dose and 14 the 0.5-mg · kg⁻¹ · h⁻¹ dose before two failures occurred. Failure was observed in only one of 21 patients at the dose of 1 mg · kg⁻¹ · h⁻¹. aPTT (±SEM) levels increased to 62±5, 76±2, and 98±3 seconds at the three doses, with minimal intraindividual variation, and Hirulog plasma levels to 1050, 2100, and 4200 mg/mL, respectively. Fibrinopeptide A plasma levels decreased at all doses but more consistently at the dose of 1 mg · kg⁻¹ · h⁻¹. The overall clinical success rate was 87.5%: 66% (3/5) at the low dose, 86% (12/14) at the intermediate dose, and 95% (20/21) at the high dose. No deaths, myocardial infarctions, or bleeding complications occurred.

Conclusions. In unstable angina patients, Hirulog infusions quickly and reproducibly yield stable, dose-dependent anticoagulant and antithrombotic effects with a favorable clinical efficacy profile. (Circulation. 1993;88[part 1]:1495-1501.)

Key Words • angina • thrombosis • Hirulog

Thrombus formation, triggered by the disruption of an atherosclerotic plaque, plays a fundamental role in the pathophysiology of acute ischemic coronary events.1,2 Accordingly, heparin3-4 and aspirin5-7 reduce the complication rate of unstable angina. Heparin, however, has important limitations: its dose-response relation is unpredictable, necessitating close monitoring.8 Antithrombin III or heparin cofactor II are needed for its inhibiting effects on the serine proteases. Available data also suggest that thrombin bound to fibrin is relatively protected from inhibition by antithrombin III and heparin-antithrombin III.8,9 The direct thrombin inhibitors such as hirudin and synthetic peptides do not need cofactors, are not known to be affected by circulating inhibitors, and are active in blocking the actions of clot-bound thrombin.9,10 Experimental studies have shown that these products can prevent the formation of a platelet-rich thrombus11,12 and facilitate thrombolysis better than heparin.13,14

The goal of this study was to investigate the potential of Hirulog in the management of unstable angina. Hirulog is a 20-amino-acid synthetic peptide that binds to thrombin's catalytic site and anion-binding exosite.15 In the first part of the study, the best doses to inhibit coagulation and thrombin generation were assessed in individual patients. In the second part, these doses were applied to the management of the acute phase of unstable angina, monitoring the clinical response and the anticoagulant and antithrombotic effects of the drug.

Methods

Study Population

Patients admitted to the Coronary Care Unit of the Montreal Heart Institute with a clear diagnosis of unstable angina or non–Q-wave myocardial infarction were considered for the study. Unstable angina was defined as an accelerating pattern of chest pain with one
or more episodes at rest ≥ 5 minutes in duration within the previous 24 hours. All patients had coronary artery disease documented by either a previous myocardial infarction, previous coronary arteriography, or transient ST-T changes on admission or during chest pain. Exclusion criteria included coronary angioplasty or coronary bypass surgery within the previous 6 months, bleeding disorders, previous hemorrhagic stroke, intracranial bleeding or transient cerebral ischemic attacks, uncontrolled hypertension (>180/110 mm Hg), serum creatinine levels >180 mmol/L, childbearing potential, or thrombolytic therapy within the previous 24 hours. Aspirin use was allowed.

The study was approved by the Institutional Review Board, and informed written consent was obtained from each patient.

**Study Protocol**

The acute dose-finding study was first performed in 15 patients using escalating doses of Hirulog. The initial dose of 0.02 mg·kg⁻¹·h⁻¹ was increased every 30 minutes to 0.05, 0.1, 0.25, and 0.5 mg·kg⁻¹·h⁻¹ for a total infusion period of 150 minutes. No intravenous bolus was given.

The second part of the study was designed to investigate whether the anticoagulant and antithrombotic effects were sustained and the potential of the drug to prevent the complications of unstable angina. The initial dose selected, 0.25 mg·kg⁻¹·h⁻¹, was the one that consistently prolonged activated partial thromboplastin time (aPTT) values and inhibited fibrinopeptide A plasma levels by 50% or more in the first study. The protocol was subsequently designed so that the dose was increased when two patients failed clinical control of unstable angina. The goal was to achieve a success rate of 95% or more without untoward side effects. This protocol design implied an unequal number of patients receiving the various doses, with more patients likely to receive the higher doses.

**Clinical Events**

Clinical success was defined as the absence of hemodynamic deterioration, a new myocardial infarction, or recurrent spontaneous ischemic pain. The diagnostic criteria for myocardial infarction were chest pain lasting 20 minutes or more with ECG changes and doubling of the patient baseline cardiac enzyme levels. Recurrent ischemia was defined as chest pain with ECG changes despite standard medical treatment, including intravenous nitroglycerin and either a β-blocker, a calcium antagonist, or a combination of the two. The ECG changes considered significant were transient ST segment depression (≥0.5 mm), ST segment elevation (≥1 mm), T-wave inversion, or pseudonormalization of previously negative T waves. The choice of the antianginal medication during the study period was left to the discretion of the treating physician. Heparin use was allowed after the discontinuation of Hirulog; it was recommended to delay its start by 4 hours.

Special care was taken during the two phases of the study to detect any bleeding or any other adverse reaction related to the drug. Patients were evaluated clinically twice daily. Hemoglobin, hematocrit, platelet counts, and liver function tests were obtained before initiation of Hirulog, daily during treatment, and 24 to 48 hours after discontinuation of the drug. Blood samples were also obtained in 21 consecutive patients 1 and 4 weeks after the study to assess whether antibodies to Hirulog had developed.

**Laboratory Analyses**

The aPTT, fibrinopeptide A, and Hirulog plasma levels were obtained in the acute study at baseline, before each dose increment, and 30 minutes and 2 hours after discontinuation of the drug. To avoid multiple venous punctures in a short period of time, a Teflon vascular sheath 14 cm long was introduced percutaneously by direct puncture of the right femoral vein. Blood was withdrawn through a new introducer inserted into the vascular sheath before each sampling. The presence of an indwelling catheter in the circulation can activate the coagulation system and be a source of thrombin generation other than the disease process itself.

In the second protocol, samples were obtained without vascular compression by direct and careful venipuncture of a forearm vein opposite the site of Hirulog infusion with a 21-gauge needle. Samples were obtained at baseline, 2 hours after initiation of treatment, daily during the infusion period, and 2 and 4 hours after the discontinuation of Hirulog.

*aPTT*. In the acute study, a bedside monitoring technique measuring aPTT in whole fresh venous blood was used (Coagulation Monitor, Ciba-Corning Diagnostics Corp, Medfield, Mass). In the second protocol, aPTTs were measured with a commercially available kit (Coatest Heparin; Kabi Diagnostica, Mölndal, Sweden) and the Automated Coagulation Laboratory (Fisher Scientific, Milan, Italy).

**Fibrinopeptide A.** After the first few drops of free-running blood were discarded, nine parts of venous blood (3.6 mL) were withdrawn into a polypropylene syringe containing one part (0.4 mL) of the anticoagulant solution recommended by the manufacturer, which contains citrate, heparin, and specific inhibitors of the serine proteases. After centrifugation at 3000 rpm for 15 minutes, 1 mL of the supernatant plasma was frozen at -70°C. Quantitative determination of fibrinopeptide A was done by the enzyme sandwich-type immunoassay technique in plasma after absorption of fibrinogen by bentonite (Asserachrom FPA, Diagnostica Stago, Asnières-sur-Seine, France). All samples from the same patient were analyzed in batch with the same kit. Normal plasma fibrinopeptide A values in our laboratory are 2.94±0.66 (SD) ng/mL. Values >50 ng/mL were counted as 50 ng/mL.

**Hirulog plasma levels.** Drug levels were measured by an inhibitory enzyme immunoassay using a highly specific murine anti-Hirulog monoclonal antibody. This assay is sensitive to Hirulog concentrations of >66 ng/mL with a coefficient of variation of <15% with repeated analysis on the same sample at concentrations of 200 ng/mL and higher. The mean of four or more determinations for each sample was used.

**Statistical Analysis**

The characteristics of the study patients were compared by χ² and t test statistics. The correlation coefficients between doses infused and blood test analyses were made by the best-fit method. The Hirulog and
### Clinical Characteristics of the Study Population Receiving Hirulog at Increasing Doses

| No. of patients | Acute Study, 0.02 to 0.5 mg · kg⁻¹ · h⁻¹ | 72-Hour Study
<table>
<thead>
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<tr>
<td></td>
<td>0.25 mg · kg⁻¹ · h⁻¹</td>
<td>0.50 mg · kg⁻¹ · h⁻¹</td>
</tr>
<tr>
<td>No. of patients</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Age, years</td>
<td>62.3±1.7</td>
<td>45.4±3.9</td>
</tr>
<tr>
<td>Clinical characteristics, n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Current smokers</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Previous MI</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Previous PTCA</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>
| Angiographic characteristics, n
| Left main or equivalent disease | 3 | 0 | 3 | 2 |
| Multivessel disease | 14 | 3 | 6 | 12 |
| Ejection fraction <50% | 2 | 2 | 4 | 3 |
| Concomitant therapy, n
| Aspirin     | 15 | 5 | 14 | 18 |
| Intravenous nitroglycerin | 1 | 2 | 7 | 14 |
| Oral nitrates  | 0 | 2 | 3 | 3 |
| β-Blockers    | 8 | 5 | 13 | 16 |
| Calcium antagonists | 7 | 3 | 6 | 12 |
| Double therapy | 3 | 3 | 7 | 9 |
| Triple therapy | 1 | 1 | 3 | 5 |

MI indicates myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass surgery.

*Coronary angiography was performed in 14 patients in the acute study and 35 in the 72-hour study.

fibrinopeptide A values were log-transformed because of a nonnormal distribution. Laboratory values were compared by ANOVAs with unbalanced repeated measures and Levene statistically equal variability among values using the BMDP Statistical Software (5V). The intragroup variability of the Hirulog plasma levels and of the aPTTs on treatment were evaluated by calculating the respective coefficients of variation. The distributions of the clinical events with the various doses used were compared by a two-tailed Fisher's exact test computed by the method of Mehta and Patel. Data are expressed as mean±SEM. A value of P<.05 was considered statistically significant.

### Results

#### Study Population

The demographic and clinical characteristics of the 55 patients enrolled in the two protocols are listed in the Table. Most of the patients were men (71%), and most (89%) underwent coronary arteriography. Left main or left main equivalent disease was found in 11% of the patients and multivessel disease in 64%, indicating that the population was at high risk. Ejection fraction was <50% in 20% of the patients.

Concomitant therapy during the 72-hour treatment study included aspirin in 37 of the 40 patients, intravenous nitroglycerin in 23, oral nitrates in 8, β-blockers in 34, and calcium channel blockers in 21. There was a trend toward more intravenous nitroglycerin use in the high-dose group (NS). Combined therapy with two antianginal drugs was administered in 19 of the patients and with three antianginal drugs in 9. None of the intergroup differences approached statistical significance. All patients with clinical failure and recurrence of chest pain were on intravenous nitroglycerin plus either a β-blocker, a calcium antagonist, or a combination of the two. The 3 patients not taking aspirin were in the group with the high dose of Hirulog. The aspirin was stopped at hospital admission in 2 of them because surgery was planned; the third patient had a history of aspirin allergy.

#### Acute Study

The aPTT, fibrinopeptide A, and Hirulog plasma levels at the different infusion doses of Hirulog are illustrated in Fig 1. A close linear correlation between drug doses and aPTT prolongation was found (r = .95). The relation with both the Hirulog and the fibrinopeptide A plasma levels was exponential and best expressed by a semilogarithmic fit (r = .91 and .96, respectively). Infusions of 0.25 mg · kg⁻¹ · h⁻¹ resulted in detectable plasma levels of Hirulog in all patients. The baseline
fibrinopeptide A plasma levels were above normal in all but one patient, with a mean of 32.5 ng/mL. These values decreased at all doses of Hirulog, including the lowest, with statistically significant decreases at doses of 0.25 mg and higher ($P<.01$).

No bleeding and no allergic reactions were observed during this protocol. At a dose of 0.5 mg·kg$^{-1}$·h$^{-1}$, one patient experienced an episode of chest pain with ECG changes, which was promptly relieved by a bolus of 100 μg of intravenous nitroglycerin.

**Treatment Study**

The protocol feature of increasing the infusion rate when 2 patients experienced failure at a given dose resulted in 5 patients receiving the 0.25-mg·kg$^{-1}$·h$^{-1}$ dose and 14 patients the 0.5-mg·kg$^{-1}$·h$^{-1}$ dose. The end point of 95% success was achieved at a dose of 1 mg·kg$^{-1}$·h$^{-1}$, with only 1 of 21 patients failing therapy.

The means of serial aPTT values obtained and the individual values for all patients at 2, 24, 48, and 72 hours on treatment are shown in Fig 2, top, and the fibrinopeptide A plasma levels obtained before, during, and after the infusion of the drug in Fig 2, bottom. Peak aPTT prolongation was reached at the first determination, 2 hours after the start of the infusion. The aPTT levels thereafter remained stable, with no significant intraindividual variation; the coefficients of variation were 11.9% at a dose of 0.25 mg·kg$^{-1}$·h$^{-1}$, 6.2% at 0.5 mg·kg$^{-1}$·h$^{-1}$, and 8.0% at 1 mg·kg$^{-1}$·h$^{-1}$. The results were also predictable, with interindividual coefficients of variation of 20%, 11%, and 13%, respectively. After discontinuation of Hirulog, the aPTT levels fell to a ratio of less than two times control values at 2 hours and to control values at 4 hours.

The fibrinopeptide A plasma levels also decreased at all doses. The response was less predictable in the low-dose group, which, however, included fewer patients. The 1.0-mg·kg$^{-1}$·h$^{-1}$ dose maintained the fibrinopeptide A levels most reproducibly within the normal range throughout the study. This high dose also resulted in significantly lower values compared with the medium dose 4 hours after discontinuation (8±2.1 versus 11.5±2.3 ng/mL, $P<.05$).

**Hirulog Plasma Levels**

The Hirulog plasma levels obtained during the infusion at 24 and 48 hours and 2, 4, and 24 hours after the
discontinuation of Hirulog are shown in Fig 3. These values were very stable during the infusion period at all three doses and correlated closely with the amount of Hirulog infused: a dose of 0.25 mg \cdot kg^{-1} \cdot h^{-1} resulted in plasma levels of 1050 ng/mL; these doubled to 2100 ng/mL with a dose of 0.5 mg \cdot kg^{-1} \cdot h^{-1} and again to 4200 ng/mL with a dose of 1 mg \cdot kg^{-1} \cdot h^{-1}. These peak values were higher than those observed with the short 30-minute infusion of Hirulog at equivalent doses. Hirulog was rapidly cleared from the plasma after discontinuation of the infusion, and plasma levels decreased to 611 ng/mL after 2 hours and to 294 ng/mL at 4 hours after discontinuation of the 0.5 mg \cdot kg^{-1} \cdot h^{-1} dose and to 1085 and 534 ng/mL, respectively, after cessation of the 1 mg \cdot kg^{-1} \cdot h^{-1} dose. The intraindividual coefficient of variation observed in this study was 11.1\% with the three doses.

Clinical Evolution

No deaths or myocardial infarctions occurred during infusion of the drug or during the subsequent period of hospitalization in patients receiving a prolonged infusion. Recurrent chest pain during the infusion period occurred in 5 of 40 patients, representing an overall success rate of 87.5\%. It is not possible to determine whether there was a dose response, given the design of the study. However, only 1 of 21 patients at the high dose had an event, representing a success rate of 95\%. This group was not size-limited by events and may be used to estimate an event rate. The probability value for the intergroup difference at the three doses was P=.07. In 1 patient receiving the 0.5 mg \cdot kg^{-1} \cdot h^{-1} dose, the ischemia was severe enough to require intra-aortic balloon counterpulsation and urgent surgery.

The aPTT values at the time of chest pain were 52 and 44 seconds, respectively, in the two patients with failure at a dose of 0.25 mg \cdot kg^{-1} \cdot h^{-1}, 60 and 71 seconds in the two patients failing the dose of 0.5 mg \cdot kg^{-1} \cdot h^{-1}, and 103 seconds in the patient with recurrent angina at the dose of 1 mg \cdot kg^{-1} \cdot h^{-1}. Three of these five patients maintained high fibrinopeptide A plasma levels during the drug infusion, and three had a secondary increase 4 hours after discontinuation of Hirulog.

No myocardial infarction or severe refractory angina developed after discontinuation of Hirulog in this study. However, ischemic chest pain occurred within the first 24 hours after discontinuation of the study drug in 2 patients (40\%) with the low dose, 4 (29\%) with the medium dose, and 1 (5\%) with the high dose; this incidence was significantly less (P<.05) with the high dose compared with the two other doses. Surgery was performed at a later time during hospitalization in 14 patients and coronary angioplasty in 9. The procedure was considered urgent because of the unstable clinical status in 1 patient at the low dose, 2 at the medium dose, and 1 at the high dose. Heparin was initiated in 16 patients usually 4 hours after the discontinuation of Hirulog, but within 1 hour in 3 patients at the medium dose and in 1 patient at the high dose. The mean duration of hospitalization after discontinuation of the study drug was 3 days in medically treated patients and 6 days in patients with coronary angioplasty.

Adverse events recorded during the study drug infusion consisted of headache in 16 patients, 14 of whom were receiving concurrent intravenous nitroglycerin. Three patients complained of transient nausea, and another patient had an episode of vomiting. No allergic reactions occurred. The only bleeding detected was occult blood in the stool of 1 patient at the dose of 0.5 mg \cdot kg^{-1} \cdot h^{-1} and of 2 patients at the dose of 1 mg \cdot kg^{-1} \cdot h^{-1}, with no fall in blood hemoglobin. It was not known whether these findings were present before Hirulog administration. Two days after discontinuation of Hirulog, 1 of these patients had a gastrointestinal hemorrhage while being treated with intravenous heparin and oral aspirin. No antibodies to Hirulog could be detected 1 and 4 weeks after its use.

Discussion

These first dose-finding studies of Hirulog in unstable angina were designed to identify the optimal dose range and to evaluate the clinical potential of this drug. Hirulog used at incremental doses resulted in rapid, dose-related prolongation of the aPTT and coincident decreases in fibrinopeptide A plasma levels. These anticoagulant and antithrombotic properties were maintained at a stable level throughout the 72-hour infusion period, with no need for dose adjustment. Hirulog also demonstrated an overall promising clinical efficacy and tolerability profile, particularly because a dose of 1 mg \cdot kg^{-1} \cdot h^{-1} controlled the unstable clinical state in nearly all patients. Additional studies are warranted to reproduce these results and to verify the optimal dose that will be useful in most patients.

Functional Properties of Hirulog

Hirulog [D-Phe-Pro-Arg-Pro-(Gly)\_2-Asn-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu] is a synthetic 20-amino-acid bifunctional antithrombin combining the catalytic site and hirudin-like exosite antithrombin peptides.13 This structure reproduces the physiological effects of natural hirudin derived from the medicinal
Hirulog produces a direct equimolar inhibition of thrombin without the need for a cofactor, as for heparin. In vitro, Hirulog (but not heparin) inhibits thrombin bound to fibrin, like other specific antithrombins such as hirudin, hirugen, and PPACK. Experimental studies have also shown that the anticoagulant effects of Hirulog, as measured by aPTT, were unaffected by the presence of platelets in the clotting environment; in contrast, the activity of heparin is reduced under these circumstances. These properties of Hirulog may represent distinct advantages in patients with unstable angina, allowing more complete control of thrombus development at the site of plaque rupture and possibly also inhibiting the thrombogenicity of thrombin entrapped within the thrombus. Experimental studies in baboons have documented that recombinant hirudin and Hirulog but not heparin inhibited the formation of arterial thrombus on endarterectomized aortic segments, collagen surfaces, and prosthetic vascular grafts. Also, recombinant hirudin prevented the acute platelet-rich thrombus formation and the restenosis seen after deep arterial injury induced by angioplasty in pigs and rabbits. In association with recombinant tissue-type plasminogen activator, Hirulog accelerated thrombolysis and delayed reocclusion in animals better than heparin and aspirin.

In human volunteers, Hirulog was well tolerated and produced stable and consistent prolongation of aPTT, with no apparent interaction with aspirin. The results of these phase 1 studies have provided the basis for the present investigation in patients with unstable angina.

Anticoagulant Effects

A close and linear relation was observed between the dose of Hirulog infused, plasma levels, and prolongation of aPTT. Even without a loading dose, the onset of action was rapid. The aPTT prolongation observed after 30 minutes in the acute dose-ranging study was of the same magnitude as that observed after 2 and 24 hours of infusion in the 72-hour study at similar doses. Plasma levels, however, were lower. The effects were also rapidly reversible, with decreases in aPTT to 45.6±1.6 seconds 2 hours after discontinuation of the prolonged perfusion and to 35.7±1.1 seconds by 4 hours with similar decreases in Hirulog plasma levels, in accordance with the short half-life of the drug when administered intravenously.

The variability of aPTT levels within a given patient during Hirulog infusion was found to be very low. Thus, close monitoring of aPTT during treatment appeared not to be required. In contrast, aPTT must be followed closely in patients receiving heparin infusions because of the nonlinear dose-response relation of this drug, caused in part by wide interpatient variabilities in heparin-neutralizing plasma proteins and in rates of heparin clearance. In a preliminary report, we noted that angina episodes that occurred during heparin therapy in unstable angina patients occurred at a mean aPTT of 46±10 seconds, whereas aPTT during ischemia-free periods and the aPTT of angina-free patients averaged 55±6 and 54±5 seconds, respectively (P<.01). These findings suggest that Hirulog might control ischemic episodes in unstable angina better than heparin.

Although the variability of aPTT levels within a given patient was low, the variability among patients was slightly higher, indicating that at least one aPTT measurement is required 30 minutes to 2 hours after the onset of treatment if a target value of aPTT is preset. However, at Hirulog doses of 0.5 and 1 mg·kg⁻¹·h⁻¹, the means of the aPTTs of all patients were >2.5 times control values. The optimal aPTT range for maximal therapeutic efficacy remains to be established and is not necessarily the same as for heparin because the mechanisms of action of the two drugs differ. Whether aPTT is the best measurement to monitor Hirulog therapy remains to be established. From our fibrinopeptide A and clinical data, it would appear that doses of at least 0.5 and 1 mg·kg⁻¹·h⁻¹ may be optimal in the higher-risk patient with coronary disease.

Antithrombotic Effects

Fibrinopeptide A, formed by the cleavage of the fibrinogen molecule by the action of thrombin, is a sensitive marker of thrombin generation in vivo. Plasma levels are generally high in unstable angina, but the short half-life of the fibrinopeptide, the variable activity of the disease process among patients, and the nonuniform timing of sampling in relation to ischemic episodes limit the sensitivity of fibrinopeptide A plasma levels as a test to confirm unstable angina. In our acute dosing study of 15 patients, the intravascular catheter positioned in the femoral vein represented a source of thrombin generation in addition to the intracoronary disease process. Nichols et al. have documented that such an intravascular catheter resulted in systemic thrombin activation with elevated fibrinopeptide A plasma levels in blood withdrawn from a distant vein. The indwelling catheter in this study served as an additional source of thrombin generation to test the antithrombotic efficacy of Hirulog. Despite this additional stimulation, Hirulog reduced thrombin generation at all doses, with a significant effect at ≥0.25 mg·kg⁻¹·h⁻¹.

In the 72-hour study, the fibrinopeptide A blood levels were obtained by atraumatic puncture to reflect endogenous thrombin generation. Levels decreased at all doses but most consistently to the normal range at a dose of 1 mg·kg⁻¹·h⁻¹. This dose also resulted in significantly less secondary elevation in fibrinopeptide A levels after discontinuation of Hirulog. The clinical significance of these posttreatment elevations is unknown, however. All together, the observations in this study suggest that doses of Hirulog that prolong aPTT to 100 seconds could be more effective in unstable angina than doses yielding the aPTT levels that are therapeutic with heparin. Clinical success at the 1-mg·kg⁻¹·h⁻¹ dose appeared superior, but the small number of patients makes this point difficult to assess.

Clinical Effects

The clinical part of this study has obvious limitations: the sample size was small, the study was unblinded, and there were no control subjects. However, the aims of the study were to determine the optimal dose range within the margins of safety. The dose was increased when two patients failed at a given level. The study population was at high risk, as documented by the severity of the underlying coronary lesions and the high rate of clinical events in those receiving the lower doses of Hirulog. A success rate, 95%, was achieved with a dose of 1
mg \cdot kg^{-1} \cdot h^{-1}. The study design is not optimal to demonstrate efficacy because of the unequal sizes of the treatment groups. However, for comparison, the event rate in 121 unstable angina patients treated in our institution with aspirin and antiangiinal drugs was 16.5% in a previous study.\textsuperscript{4} The better clinical results observed at higher plasma levels are comparable to observations in the porcine model of deep arterial injury, in which inhibition of thrombus formation required hirudin levels 8 to 10 times higher than levels needed to prevent thrombus formation at sites of mild arterial injury.\textsuperscript{11} Further, significantly fewer patients had recurrence of angina after discontinuation of Hirulog in the high dose compared with the low and medium doses. No patient, however, had severe rebound, which agrees with our previous observation that treatment with aspirin and an anticoagulant is not associated with rebound compared with an anticoagulant alone.\textsuperscript{22} In this study, all patients received aspirin before discontinuation of Hirulog except the patients in whom surgery was planned; heparin was then continued up to the time of surgery.

Hirulog was well tolerated in our patients, with practically no bleeding complications despite concomitant aspirin therapy. The occult blood in the stool of three patients may have been present before Hirulog administration and was associated with a gastrointestinal hemorrhage in one patient during heparin therapy after the cessation of Hirulog. The other adverse effects noted were minor and were probably related to concomitant medication, particularly intravenous nitroglycerin.

In conclusion, the excellent safety profile of Hirulog, its ease of administration compared with heparin, its antithrombotic effect as documented in this study, and its favorable clinical activity at the 1-mg \cdot kg^{-1} \cdot h^{-1} dose are promising and provide the basis for a larger-scale study to directly compare Hirulog with standard antithrombotic therapy in unstable angina.

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