Relative Efficacy of Antithrombin Compared With Antiplatelet Agents in Accelerating Coronary Thrombolysis and Preventing Early Reocclusion

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Background. Optimal coronary thrombolysis should be prompt and persistent. Although activation of platelets and increased thrombin activity have been associated with clinical thrombolysis, the role of each in delaying thrombolysis or inducing early coronary reocclusion has been difficult to define.

Methods and Results. In conscious dogs with coronary thrombosis induced by electrical current, we assessed the impact on the rapidity of thrombolysis and the incidence of reocclusion of two types of adjunctive treatment given concomitantly with intravenous tissue-type plasminogen activator (t-PA): 1) inhibition of platelet function with a peptide mimetic antagonist of platelet glycoprotein IIb/IIIa receptors or with lysine acetylsalicylic acid (ASA) and 2) inhibition of thrombin activity with recombinant hirudin or with heparin. ASA but not the receptor antagonist shortened the time to thrombolysis with t-PA (20±13 [mean±SD] minutes with ASA, 36±15 minutes with receptor antagonist, and 43±16 minutes with the saline control). Reocclusion occurred promptly after completion of the infusion of t-PA in all seven dogs given saline. Reocclusion was delayed and prevented in some dogs within 90 minutes after the end of the infusion of t-PA by both antiplatelet agents but still occurred in 42% despite continued inhibition of platelet function (i.e., three of six dogs given ASA and two of six given receptor antagonist). In contrast, inhibition of thrombin activity with recombinant hirudin in a dose that prolonged the partial thromboplastin time modestly (1.5–2-fold) resulted in accelerated lysis (19±10 minutes) and prevention of reocclusion in each of six dogs. Heparin given in doses that elicited similar prolongation of the partial thromboplastin time did not accelerate lysis nor prevent reocclusion, which occurred in five of six dogs.

Conclusions. Inhibition of thrombin by recombinant hirudin facilitates thrombolysis and maintains patency of coronary arteries recanalized with t-PA particularly effectively. The benefit conferred may reflect direct anticoagulant effects plus diminished activation of platelets secondary to decreased thrombin activity. (Circulation 1991;83:1048–1056)

Although thrombolytic agents such as tissue-type plasminogen activator (t-PA) elicit recanalization of up to 80% of thrombatically occluded coronary arteries,1,2 early reocclusion occurs in approximately 19% of successfully recanalized vessels.3,4 Adjunctive antithrombotic agents may improve early patency rates and prevent reocclusion.4,5 However, early reocclusion occurs despite concomitant administration of conventional agents including heparin and aspirin.6–9 Early reocclusion may result, in part, from activation of platelets, as has been demonstrated clinically.10,11 Augmentation of thrombin activity has been shown also to accompany thrombolysis,12,13 possibly reflecting a paradoxical prothrombotic effect of plasminogen activators attributable to elaborated plasmin that may contribute to reocclusion.14 Because the relative contribution to reocclusion of activated platelets and of thrombin activity per se has not been delineated, it is not yet clear whether thrombolysis can...
be best facilitated with powerful antiplatelet agents, powerful antithrombin agents, or both.

Highly specific antiplatelet and antithrombin agents have been developed recently. We15 have shown that arginine-glycine-aspartate-o-methyltyrosine amide (SC 46749), a tetrapeptide analogue of the adhesive protein recognition sequence Arg-Gly-Asp (RGD) that potently inhibits binding of fibrinogen to platelet glycoprotein (GP) IIb/IIIa receptors, prevents reocclusion caused by platelet-rich thrombi after thrombolysis in the femoral arteries of dogs. Others16,17 have demonstrated that desulfatohirudin (CGP 39393), produced by recombinant DNA technology, reacts specifically with thrombin to form an inactive enzyme-inhibitor complex and, unlike heparin, does not require antithrombin III for inhibitory activity.

The present study was designed to determine whether inhibition of platelet function (with a peptide mimetic analogue of the RGD recognition sequence of platelet GPIIb/IIIa receptors or an analogue of aspirin) or inhibition of thrombin activity (with recombinant hirudin or heparin) is more efficacious for prevention of early reocclusion after coronary artery thrombolysis with t-PA. Because of the recognized importance of rapid coronary arterial recanalization for optimal salvage of ischemic myocardium,18 we characterized as well the interval to thrombolysis and its modification by these agents when administered concomitantly with t-PA.

Methods

Animal Preparations

All procedures were conducted according to the guiding principles of the American Physiological Society and were approved by the animal studies committee at Washington University, St. Louis. Mongrel dogs weighing 19–26 kg were premedicated with acepromazine maleate (0.5 mg/kg s.c.) and atropine sulfate (0.04 mg/kg s.c.) after an overnight fast. Anesthesia was induced with thiopental (15 mg/kg i.v.) and maintained with halothane (1.4%) in oxygen delivered by a mechanical ventilator. Catheters were placed aseptically in a common carotid artery and an external jugular vein. The heart was exposed through a left thoracotomy in the fourth intercostal space and a pericardial incision. A segment of approximately 2 cm of the left anterior descending coronary artery above the midventricular diagonal branch was dissected free from surrounding tissue. Small side branches of the left anterior descending coronary artery were ligated. A 20-MHz Doppler flow probe (purchased from Craig Hartley, PhD, Baylor College of Medicine, Houston) was placed around the vessel proximally. Distal to the flow probe, a needle electrode consisting of the tip (1 cm) of a 23-gauge needle crimped on the end of a 6-cm length of 30-gauge Teflon-insulated silver wire (model 7875, A-M Systems, Everett, Wash.) was inserted obliquely approximately 3 mm into the arterial lumen. The needle was stabilized on either side of the vessel with 5-0 prolene sutures through the epicardium. The other end of the silver wire was bent in an “S” shape to reduce the stress on the needle connection, soldered to a 60-cm length of hookup wire (model 36F1727WA-9, Newark Electronics, Maryland Heights, Mo.,) and sutured to the epicardium. To increase durability of the electrode and to prevent leakage of current to the surrounding tissue, heat-shrink tubing was applied over the needle/wire and soldered connections. A ground wire was sutured to the subcutaneous tissue to complete the electrical circuit. The ground wire, electrode lead wire, and Doppler flow probe wires were brought through the chest wall, tunneled subcutaneously, and exteriorized dorsally. The chest was closed in layers and evacuated with a chest tube. Dogs were given a suspension of penicillin G benzathine and penicillin G procaine (0.1 ml/kg s.c.) daily for 3 days and morphine sulfate as needed to relieve pain. Catheters were flushed with saline, and the catheter dead space was filled with heparinized saline (100 units/ml) every other day after surgery.

Experimental Protocol

Five to 7 days after surgery, the dogs were sedated lightly with morphine sulfate (0.4 mg/kg i.v. followed by 0.2 mg/kg as needed) and placed in a supporting sling that induced no apparent discomfort. The electrocardiogram, arterial pressure, and mean and phasic flow velocity in the left anterior descending coronary artery were monitored continuously. Thrombosis was induced by applying a current of 200 μA through the coronary electrode connected in series with the positive terminal of a 9-V battery, an ammeter, a 20-kΩ resistor, and a 50-kΩ potentiometer. Delivery of current was maintained until persistent, complete thrombotic occlusion had occurred, reflected by zero-flow velocity. Occlusion was almost always preceded by cyclic flow variations consisting of a gradual decrease in flow velocity followed by an abrupt increase, analogous to flow variations attributable to intermittent accumulation and dislodgment of platelet thrombi.19

Beginning 1 hour after persistent coronary occlusion, human recombinant t-PA (Activase, Genentech, South San Francisco) was infused intravenously at a rate of 17 μg/kg/min for 60 minutes (total dose, 1 mg/kg). Successful recanalization was defined prospectively as a return of mean flow velocity to at least 50% of the baseline value. Lidocaine (60 mg i.v.) was given immediately after recanalization and as needed thereafter for suppression of ventricular tachyarrhythmias.

Dogs were assigned randomly before each study to treatment with one of four adjunctive agents or saline (control) (Table 1) as follows: group 1, lysine acetylsalicylic acid (ASA, Lorex Pharmaceuticals, Skokie, Ill.), a water-soluble analogue of aspirin; group 2, a GPIIb/IIIa receptor antagonist (SC 47643, Monsanto/Searle, St. Louis), which is a peptide mimetic analogue of RGD that potently inhibits binding of
The minimal (threshold) concentration of collagen resulting in an irreversible increase in light transmission of greater than 50% was estimated in serial assays with samples supplemented to contain final concentrations of collagen of 0.7, 1.4, 2.8, 5.6, and 11.1 μg/ml.

Platelet counts in whole blood were determined by hemocytometry before the administration of adjunctive agents and at the end of each experiment. Hematocrits were measured with a conductivity analyzer (NOVA Biomedical, Waltham, Mass.) in samples collected before initiation of thrombosis and at the end of each experiment. In selected dogs, the PTT and prothrombin time were assessed with the use of a Coag-A-Mate XC automated coagulation timer (Organon Teknika, Durham, N.C.) in samples collected at the same intervals as those used for platelet function studies. Buccal mucosa bleeding times were performed by the method of Jergens et al21 with the use of a Simplate II device (Organon Teknika).

**Statistical Analysis**

Results are expressed as mean±SD. Fisher’s exact test and standard survival analysis with the use of a log-rank test22 were used to compare the incidence of reocclusion between groups. Analysis of variance for repeated measures was used to assess time-dependent changes in coronary flow velocity, heart rate, and blood pressure and to determine whether changes in one group were equivalent to corresponding changes over the same interval in other groups. A Wilcoxon test was used to assess differences between groups in the frequency of cyclic flow variations and to test the hypothesis that changes in platelet counts and hematocrit after administration of adjunctive agents were equivalent to corresponding changes in the control group. The relation between the interval required for recanalization and the interval preceding reocclusion was assessed by Pearson’s correlation. Student’s t test was used to compare mean intervals to recanalization in dogs with and without coronary recocclusion. A value of p<0.05 was considered indicative of a significant difference.

**Results**

Complete coronary occlusion was induced with the application of electrical current in 35 dogs. Two developed ventricular fibrillation before adjunctive treatment could be initiated and were excluded. Among the surviving 33 dogs, the interval from the initiation of current to the onset of complete occlusion did not differ appreciably among treatment groups (190±110, 170±65, 215±84, 311±164, and 139±122 minutes for groups 1–5, respectively); the exception was group 4, in which the mean interval was increased by delayed but stable occlusion (533 minutes) in one dog.

All dogs given t-PA exhibited arterial recanalization with return to at least 50% of the baseline flow velocity; nearly all exhibited flow velocities of 100% or more of the baseline values. Two dogs (one each in

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**Table 1. Adjunctive Treatment Protocols**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Adjunctive treatment</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>ASA (5 mg/kg bolus)</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>Glycoprotein Ib/IIa antagonist (0.5 mg/kg/min infusion for 10 minutes, then 0.2 mg/kg/min)</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>Hirudin (1.5 mg/kg bolus, then 1.5 mg/kg/hr infusion)</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>Heparin (150 units/kg then 50 units/kg/hr after completion of the infusion of tissue-type plasminogen activator)</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>Saline (0.9%)</td>
</tr>
</tbody>
</table>

ASA, lysine acetylsalicylic acid, a water-soluble analogue of aspirin (each vial contained 0.9 g powder equivalent to 0.5 g ASA); glycoprotein Ib/IIa antagonist, guanidino-octanoyl-aspartyl-2-(4 methoxysphenyl)-ethylamide (SC 47643); hirudin, recombinant desulfatohirudin (CGP 39393), specific gravity 11.500 antithrombin units/mg; heparin, sodium heparin from porcine intestine.

fibrinogen to platelet GPIIb/IIIa receptors with an IC50 of 9.5×10⁻⁶ M for inhibition of collagen-stimulated aggregation in canine platelet-rich plasma and with an in vivo plasma half-life in dogs of 15 minutes²⁰; group 3, recombinant desulfatohirudin (CGP 39393), Ciba-Geigy, London, and Plantorgan Werk KG, Bad Zwischenahn, FRG); group 4, heparin (Elkins-Sinn, Cherry Hill, N.J.); and group 5, saline (control). Dosages of agents were selected to completely inhibit collagen-induced platelet aggregation as assessed ex vivo while prolonging the bleeding time only modestly (ASA and the receptor antagonist) or prolonging the partial thromboplastin time (PTT) 1.5-fold to twofold (hirudin and heparin). To determine whether adjunctive treatment that was initiated to inhibit platelets or thrombin in association with activation of plasminogen by t-PA could accelerate thrombolysis as well as prevent reocclusion, each adjunctive agent was administered by bolus intravenous injection or by infusion in equivalent fluid volumes or both (Table 1) beginning 15 minutes before the start of the infusion of t-PA and continuing for 90 minutes after its completion. During the 90 minutes after infusion of t-PA, the occurrence of cyclic flow variations and of persistent reocclusion (defined prospectively as zero-flow velocity persisting for at least 1 minute) was recorded.

To characterize the composition of thrombi that formed despite treatment, each dog was anesthetized, the chest was opened, and the coronary artery was ligated proximal and distal to the thrombus. The isolated arterial segment was excised and prepared for scanning electron microscopy as described previously.¹⁵

**Hematologic Studies**

Arterial blood samples were collected for evaluation of platelet aggregation ex vivo before the administration of adjunctive agents and 45 minutes after completion of infusion of t-PA. Aggregation in platelet-rich plasma was characterized as described previously¹⁵ with the use of bovine tendon collagen (Helena Laboratories, Beaumont, Tex.) as the agonist.

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groups 1 and 5) developed ventricular fibrillation after coronary reperfusion and were therefore excluded from subsequent analysis.

**Effects of Adjunctive Antiplatelet Agents on Thrombolysis and Early Reocclusion**

Concomitant administration of t-PA and ASA shortened the time to reperfusion compared with that observed with t-PA and saline (Figure 1). After infusion of t-PA had been completed, reocclusion occurred rapidly and persisted over the entire 90-minute observation interval in all seven dogs given saline alone (Figure 2). In contrast, early reocclusion was delayed and occurred ultimately in only three of six and two of six dogs given ASA and the platelet GP IIb/IIIa receptor antagonist, respectively (Figure 2). Although the incidence of reocclusion was reduced compared with that in controls only in dogs given the receptor antagonist, when the time to reocclusion was considered together with the incidence of reocclusion by use of survival analysis, a significant inhibitory effect on reocclusion was observed for both antiplatelet agents (Figure 2). Thus, early reocclusion was inhibited by antiplatelet agents, although it did occur in 42% of treated dogs. Consistent with the reduced incidence of reocclusion, the combined frequency of cyclic flow variations plus persistent reocclusion after completion of infusion of t-PA was decreased by both antiplatelet regimens compared with results in control dogs (2.0±2.7 and 2.2±3.6/hr for groups 1 and 2 compared with 25.5±19.1/hr for group 5, p<0.01).

**Effects of Adjunctive Antithrombin Agents on Thrombolysis and Early Reocclusion**

Infusion of recombinant hirudin with t-PA shortened the time to reperfusion compared with results in control dogs (Figure 1), prevented reocclusion in all six dogs treated (Figure 2), and abolished cyclic flow variations (p<0.005 compared with group 5). In contrast, heparin did not shorten the time to reperfusion (Figure 1) and was much less effective than hirudin in preventing reocclusion (p<0.02). Reocclusion occurred in five of six dogs given heparin, although it was delayed. Thus, an inhibitory effect was demonstrable by survival analysis (Figure 2). Cyclic flow variations were decreased in dogs given heparin (5.4±3.3/hr, p<0.02 compared with group 5).

**Hematologic and Hemodynamic Variables**

The hematocrit did not differ between groups at baseline (39±3%, 40±3%, 40±3%, 39±5%, and 37±4% for groups 1–5) and did not decrease significantly in any group by the end of the study. The initial platelet count in whole blood did not differ among groups. It too did not change appreciably during studies (data not shown).

The median concentration of collagen required to induce platelet aggregation in platelet-rich plasma was increased markedly in dogs that had been given ASA or the platelet GPIIb/IIIa receptor antagonist, from 2.8 and 5.6 μg/ml, respectively, before administration of the adjunctive agent to greater than 11.1 μg/ml afterward. Neither hirudin nor heparin had any effect on platelet aggregation induced with collagen in vivo.

The baseline PTT and prothrombin time averaged 12.6±1.4 and 8.1±0.8 seconds, respectively. Both hirudin and heparin prolonged the PTT modestly to 1.7 and 1.8 times baseline values, respectively (Table 2). The prothrombin time was affected less. Antiplatelet agents exerted minimal effects on these variables (Table 2). Buccal mucosal bleeding time averaged 2.6±0.4 minutes before administration of adjunctive agents; it was prolonged by aspirin (1.6...
times baseline) and by the GPIIb/IIIa receptor antagonist (2.5 times baseline) but was affected less by hirudin or heparin (Table 2).

Mean arterial pressure and heart rate measured before administration of adjunctive agents were similar in all groups (data not shown). Antithrombotic agents themselves had no effect on arterial blood pressure or heart rate. However, during the course of individual studies, a trend toward an increased heart rate was seen in all groups, possibly reflecting combined effects of initial acute ischemia, tachyarrhythmia, and mild hypovolemia. The increase in heart rate was significant only for dogs given the GPIIb/IIIa receptor antagonist (101±16 beats/min at baseline and 135±39 beats/min 90 minutes after the end of infusion of t-PA, p<0.05) and for those given heparin (88±22 beats/min at baseline and 138±26 beats/min 90 minutes after the end of infusion of t-PA, p<0.05).

The Relation Between Intervals to Recanalization and to Early Reocclusion

In dogs in which coronary reocclusion occurred, a significant inverse correlation was evident between the interval to recanalization and the interval to reocclusion (Figure 3). Furthermore, the mean interval to recanalization in dogs in which early reocclusion occurred was twice that in dogs in which it did not occur (40±18 versus 21±11 minutes, p<0.005).

![Figure 3. Plot showing relation of time to recanalization and time to reocclusion in dogs in which reocclusion occurred.](image)

Table 2. Effect of Adjunctive Agents on Hemostatic Variables

<table>
<thead>
<tr>
<th>Adjunct</th>
<th>PTT (sec)</th>
<th>PT (sec)</th>
<th>Bleeding time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hirudin (n=6)</td>
<td>1.7±0.1</td>
<td>1.4±0.1</td>
<td>1.4±0.3 (1.0–1.9)</td>
</tr>
<tr>
<td>Heparin (n=6)</td>
<td>1.8±0.3</td>
<td>1.0±0.1</td>
<td>1.1±0.3 (0.7–1.4)</td>
</tr>
<tr>
<td>ASA (n=3)</td>
<td>1.0±0.0</td>
<td>1.0±0.0</td>
<td>1.6±0.2 (1.3–1.8)</td>
</tr>
<tr>
<td>IIb/IIa antagonist (n=3)</td>
<td>0.9±0.0</td>
<td>1.0±0.0</td>
<td>2.5±0.7 (1.6–3.4)</td>
</tr>
</tbody>
</table>

Values are mean±SD and are expressed as the ratio of measurements obtained during adjunctive treatment to those before treatment. Numbers in parentheses indicate the range.

PTT, partial thromboplastin time; PT, prothrombin time; ASA, lysine acetylsalicylic acid; IIb/IIa, glycoprotein IIb/IIIa.

Morphological Characteristics of Thrombi

Scanning electron microscopy of reoccluding thrombi that had formed after initial lysis in control dogs exhibited regions of platelet-rich material near the electrode tip surrounded by heterogeneous regions rich in either platelets, fibrin, or erythrocytes (Figure 4). Thrombi in arteries that reoccluded despite administration of antiplatelet agents contained platelet aggregates around the electrode with contiguous regions rich in fibrin and erythrocytes but containing fewer platelets compared with thrombi in control dogs.

Discussion

Although coronary thrombolysis salvages myocardium and reduces mortality in patients with acute myocardial infarction,1,2,8 its benefits are limited by delayed lysis and early reocclusion in a substantial minority of treated patients.3–5,9 Clinical efficacy appears to depend not only on activation of fibrinolysis but also on inhibition of concomitant thrombosis that may retard lysis and predispose to reocclusion. Lytic agents have been shown to elicit prothrombotic effects12,14 and may activate platelets10,11 either directly by elaborating compounds that promote aggregation, including thrombin, or indirectly by releasing active thrombin from thrombi undergoing lysis.25 Therefore, concomitant anticoagulation as well as inhibition of platelet function is likely to be of paramount importance in maximizing the benefits of thrombolysis.

Even though reocclusion was often delayed in the present study, it occurred in 42% of dogs given different antiplatelet agents adjunctively with t-PA. In contrast, inhibition of thrombin with recombinant hirudin accelerated thrombolysis, prevented reocclusion throughout the 90-minute observation interval, and abolished cyclic flow variations. Heparin, in doses that prolonged the PTT comparably, was much less effective. Because of the prevention of early reocclusion by hirudin, potentially additive effects of antiplatelet agents plus hirudin could not be easily defined. Nevertheless, our results are consistent with the hypothesis that intense inhibition of thrombin may potentiate clot lysis and inhibit reocclusion by inhibiting both coagulation itself and thrombin-induced activation of platelets.
We have shown previously that either aspirin or a synthetic tetrapeptide antagonist of platelet GPIIb/IIIa receptors prevents reocclusion after thrombolysis in dogs with arterial injury induced electrically, giving rise to thrombi rich in platelets. Despite similar vascular injury in the coronary arteries of closed-chest, conscious dogs, however, neither aspirin nor a peptide mimetic analogue of RGD (exhibi-
itizing greater potency than the peptide antagonist we used previously) completely prevented coronary reocclusion. The difference between results in femoral and coronary arteries may reflect differences in rheological or vasoregulatory properties of the two types of vessels that influence the relative deposition of platelets and fibrin at the site of injury. Compared with reclosing coronary thrombi in control dogs (Figure 4), platelet content was reduced and fibrin and erythrocyte content was increased in reclosing thrombi in dogs given antiplatelet agents. We and others have shown that antiplatelet agents are considerably less effective in preventing arterial thrombosis under conditions eliciting thrombi rich in fibrin. Thus, continued deposition of fibrin despite inhibition of platelets may be one factor accounting for the failure of antiplatelet agents to completely prevent coronary reocclusion.

Our results with antiplatelet agents are consistent with results in clinical studies showing that inhibition of platelet function alone does not completely prevent coronary artery reocclusion after initially successful thrombolysis. They also agree with data showing that the RGD-containing peptide bitistatin by itself does not significantly accelerate thrombolysis or prevent reocclusion in dogs with arterial thrombosis. Nevertheless, some investigators have demonstrated that monoclonal antibodies to the platelet GPIIb/IIIa receptors prevent experimental coronary arterial reocclusion. The doses of antibodies required, however, caused marked prolongation of the bleeding time (to greater than 30 minutes in 63% of dogs) compared with the twofold to threefold prolongation of bleeding time we observed with the GPIIb/IIIa receptor antagonist (Table 2). Monoclonal antibodies may have effects on platelet function in addition to those mediated by the RGD recognition sequence of GPIIb/IIIa receptors. Regardless, because increased bleeding time associated with thrombolytic agents may be an important predictor of subsequent bleeding, alternatives to profound and irreversible inhibition of platelet function are attractive.

Inhibition of thrombin is a reasonable alternative to direct inhibition of platelet aggregation, because thrombin not only activates platelets leading to aggregation and secretion of inhibitors that may delay thrombolysis but also because it mediates fibrin formation and activation of factors V and VIII, leading to subsequent amplification of thrombin formation. However, as shown previously and confirmed in the present studies, heparin, in doses that modestly increase the PTT and bleeding time, has little effect on the incidence of reocclusion. Even doses of heparin that prolong the PTT more than sixfold fail to prevent reocclusion after thrombolysis. This may reflect the limited capacity of heparin to inhibit clot-bound thrombin, its dependence for activity on antithrombin III, or potential inhibition of its activity by platelet products including platelet factor 4.

Availability of antithrombin III–independent inactivators of thrombin such as recombinant hirudin has permitted evaluation of the effects of direct anti thrombin agents on thrombolysis. Hirudin, unlike heparin, effectively inhibits thrombin exposed on the surface of thrombi. Administration of a dose of hirudin that affected the PTT and bleeding time only modestly (Table 2) completely abolished cyclic flow variations and prevented early reocclusion after thrombolysis (Figure 2). Thus, at doses required for prevention of reocclusion, hirudin may not strongly predispose to bleeding.

Our results are consistent with those of Heras et al, who found that hirudin was more effective than heparin in reducing platelet deposition and preventing acute, mural thrombosis after angioplasty in pigs. These investigators also showed that inhibition of thrombin with hirudin was more effective than inhibition of platelet function by aspirin.

In contrast with our results, Fitzgerald and Fitzgerald found that argatroban, a synthetic antithrombin agent, did not prevent coronary reocclusion in dogs when given in doses that prolonged the PTT to the same extent as that observed by us after hirudin. Moreover, even with doses of argatroban that prolonged the PTT threefold to fourfold, reocclusion was not inhibited completely, and cyclic flow variations were not abolished. Differences between their results and ours may reflect the nature of the antithrombin agents used and the manner in which t-PA was administered. In our study, a fixed dose of t-PA was given to all dogs regardless of the actual interval to recanalization analogous to common clinical practice. Thus, infusions of t-PA were maintained for an average of 41 minutes after recanalization. Conversely, Fitzgerald and colleagues discontinued infusions of t-PA 10 minutes after recanalization in each case, at which time a residual stenosis of 80–90% could be delineated angiographically. Accordingly, in our experiments, lysis of the thrombus may have been more complete with consequently less intense predisposition to early reocclusion.

The extent of salvage of myocardium is highly dependent on the brevity of the interval between the onset of ischemia and restoration of perfusion by thrombolysis. Our results show that both aspirin and hirudin markedly shorten the interval required for induction of thrombolysis by t-PA. Neither the GPIIb/IIIa receptor antagonist nor heparin alone appeared to do so. These results are consistent with potentiation of thrombolysis in animals by aspirin and by argatroban and with the apparent failure of heparin to increase the incidence of recanalization defined angiographically 90 minutes after infusion of t-PA in patients. We observed a significant, inverse correlation between the time required for thrombolysis and the rapidity of subsequent reocclusion when it did occur (Figure 3). This trend may reflect inhibition of ongoing deposition of fibrin and platelets that could both delay
overt thrombolysis and potentiate early reocclusion. Alternatively, earlier lysis might have resulted in more complete removal of residual thrombus that could otherwise serve as a potent stimulus for reocclusion.5 Regardless, concomitant administration of specific adjunctive agents with a plasminogen activator appears likely to facilitate the maximal benefit attainable with fibrinolytic drugs.

Clinical Implications

Several pharmacological approaches for acceleration of coronary thrombolysis and reduction of coronary reocclusion have been considered.4-6,7,10,13,25,26,37-39 Prolongation of fibrinolysis appears to reduce the incidence of reocclusion but may predispose to bleeding.6,39 Although aspirin improves the outcome of thrombolysis,8 the mechanism responsible is uncertain. The efficacy of antiplatelet agents may be limited when they are administered in doses that perturb hemostatic function only moderately because reocclusion appears to involve deposition of both fibrin and platelets, perhaps reflecting effects of thrombin both on the coagulation system itself and on local activation of platelets. As is evident from our results, powerful and specific antithrombin agents, in doses that do not induce profound derangements of hemostasis, given together with a plasminogen activator appear likely to be particularly useful for achieving rapid and sustained coronary thrombolysis.

Acknowledgments

The authors thank Larry P. Feigen, PhD, at G.D. Searle for information regarding SC 47643; Steven P. Adams, PhD, at Monsanto for provision of SC 47643; Robert B. Wallis, PhD, at Ciba-Geigy for provision of recombinant hirudin; Paul Myer, DVM, Kurt Bar- ringhaus, and Bill Kraft for technical assistance; Ken Schechtmann, PhD, for statistical analysis; Carol Pellegrin at the Monsanto Microscopy Laboratory for preparation of scanning electron micrographs; and Kelly Hall for typing the manuscript.

References


**KEY WORDS** • tissue-type plasminogen activator • thrombolysis • platelets • thrombin
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Circulation. 1991;83:1048-1056
doi: 10.1161/01.CIR.83.3.1048

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1991 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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