Editorial Comment

Reperfusion, Specific Thrombin Inhibition and Reocclusion After Thrombolysis*

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Thrombosis and thrombolysis. These are dynamic and simultaneous reactions that may be mutually regulated by the relative rates of each (1). Thrombolysis by streptokinase or recombinant tissue-type plasminogen activator (rt-PA) enhances thrombosis and thrombin generation as evidenced by the increased generation of fibrinopeptide A and its suppression by heparin (1–3). Experimentally, heparin in sufficient doses can accelerate thrombolysis with streptokinase, urokinase or rt-PA (4,5). This effect appears to be a result of the antithrombin action of heparin. Heparin also induces a dose-dependent decrease in platelet, fibrinogen and thrombus deposition on the deeply injured arterial wall. The dominant role of thrombin after deep arterial injury has been documented by the total prevention of mural thrombosis and the limitation of platelet deposition to a single layer by specific thrombin inhibition. This specific therapy only inhibits platelet aggregation induced by thrombin (not that induced by prostaglandins, serotonin, adenosine diphosphate or collagen) (6,7) but is the most effective therapy so far observed for arterial thrombosis.

Different doses of heparin have not been evaluated for acceleration of thrombolysis or increased incidence of vessel patency or reperfusion in humans. Nevertheless, as suspected from known mechanisms of thrombosis and thrombolysis (8) and the long known binding of active thrombin to fibrin within arterial thrombi (9,10), heparin is necessary to prevent occlusion and to maximize vessel patency after thrombolysis with rt-PA (11,12). Indeed, previous studies (13) demonstrating superior reperfusion with rt-PA compared with streptokinase were performed during immediate and simultaneous intravenous administration of heparin.

The present study. The relative roles of heparin, specific thrombin inhibition, aspirin and glycoprotein platelet membrane receptor inhibitors as adjunctive therapy to accelerate thrombolysis and prevent reocclusion are uncertain. With use of a canine model, Yasuda et al. (14), in this issue of the Journal, provide additional information concerning acceleration of thrombolysis and reduction of early reocclusion during the first 2 h after the start of rt-PA administration with the simultaneous administration of four different adjunctive therapies: 1) intravenous aspirin alone, 2) specific thrombin inhibition with Argatroban which prolonged the mean activated partial thromboplastin time to more than six times the baseline control level, 3) both aspirin and Argatroban, and 4) monoclonal antibody 7E3-Fab' against the platelet membrane glycoprotein IIb/IIIa.

In this canine model, the coronary thrombus induced for lysis was a whole blood clot created by injecting whole blood plus thrombin into an isolated arterial segment after compressing the segment four times with a blunt forceps to induce injury. Thus, the thrombus within the injured segment is typical of a venous or whole blood clot rather than an arterial thrombus and is probably less resistant to lysis than a platelet-rich thrombus would be. Furthermore, the substrate for r thrombosis is not injured arterial wall but a whole blood clot rich in fibrin but not in platelets; the only chance for platelet enrichment of the clot is in those animals with reperfusion, which may allow additional platelet accumulation as blood at a high shear rate (15) flows through the clot. In fact, the only accurate method of assessing relative platelet richness requires isotopic labeling of platelets and fibrinogen, which was not performed in this study. Finally, the study by Yasuda et al. (14) compared the relative effects of four adjunctive therapies only in small groups of five or six dogs.

Aside from these methodologic problems, the study results are consistent with the known dominant action of thrombin in thrombosis (6,7) and the partial effect of aspirin, which is a weak or secondary platelet inhibitor that reduces but does not eliminate mural thrombosis or a significant degree of platelet deposition (16,17). Aspirin alone did not reduce time to reperfusion by rt-PA (14,18). However, thrombin inhibition with Argatroban reduced the time to reperfusion by 40% to 50%. The monoclonal antiplatelet glycoprotein IIb/IIIa antibody may have been better than aspirin in shortening the time to reperfusion (numbers of dogs were too small to evaluate data with certainty) but it caused more bleeding than aspirin and was not superior to thrombin inhibition with Argatroban (14).

Reocclusion was not prevented with Argatroban alone or with the monoclonal antiplatelet glycoprotein IIb/IIIa antibody, but its frequency was lowest when combination treat-

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ment with Argatroban plus aspirin was used (14). It is unclear whether increased doses of Argatroban may be useful and obviate the need for aspirin because a dose-response study has not been reported. Another thrombin inhibitor, hirudin, is very specific, has a longer half-life (50 to 60 min versus 5 min for Argatroban) and is essentially irreversible in its binding to thrombin (dissociation constant $10^{-13}$ versus $10^{-8}$ for Argatroban). Hirudin can totally prevent mural thrombosis and limit platelet deposition to a single layer in arteries with deep arterial injury at doses that prolong the activated partial thromboplastin time to two to three times the control level but not at lower doses (7,16). Preliminary studies in our laboratory suggest that hirudin alone may also accelerate thrombolysis of platelet-rich thrombi and lead to more thorough lysis with reduced risk for reocclusion. Because of the potent effects of hirudin in eliminating mural thrombosis and reducing platelet deposition to a single layer, no adjunctive therapy (such as aspirin) appears to be necessary for additional antithrombotic effects. Yasuda et al. (14) performed no analysis of the effect of fibrin/fibrinogen degradation products or decrease in fibrinogen levels (variables of the lytic state) on the incidence of reocclusion, as performed in patients receiving rt-PA in a clinical study (19); however, the number of dogs may be too small for such an analysis in the current study.

Role of specific thrombin inhibition to enhance thrombolysis. The necessary duration of antithrombin therapy is uncertain. Most importantly, the approach and goals may differ for prevention of thrombosis in the presence of deep arterial damage as compared with treatment of preexisting thrombus. The goal of the latter treatment is total blockade of further thrombus growth and thus enhancement of endogenous lysis. Indeed, although thrombosis takes minutes to develop, endogenous lysis takes days and may be enhanced if thrombosis is totally blocked. That is, as a thrombus is lysed from the surface into its deeper portions, active thrombin bound to fibrin is exposed and so requires continued antithrombin therapy to permit a balance in favor of lysis, with a subsequent decrease in the mural thrombus mass or with rethrombosis, or both. Because a 50 times greater dose of heparin is required to reduce the activation of fibrin-bound thrombin on clot surface compared with a specific thrombin inhibitor (20), specific thrombin inhibition is destined to play a major role for therapy of some clinical situations of arterial thrombosis. In vivo studies (6,7,21) after deep arterial injury support the superiority of specific thrombin inhibition over heparin. However, specific thrombin inhibition may not be as effective as heparin for preventing thrombosis on prosthetic materials or may require higher dosages (22). The current report (14), other previous experimental studies (23,24) and ongoing studies in our laboratory support a role for specific thrombin inhibition for the enhancement of thrombolysis. However, preclinical dose-response studies and studies over the duration of therapy for preventing the regrowth of thrombus and encouraging the continued endogenous lysis of thrombus are required. At present such studies are ongoing in American and European institutions.

References


