Pharmacologic and Clinical Characteristics of Thrombolytic Agents

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Arterial and venous thromboembolic events, including myocardial infarction, ischemic stroke, peripheral arterial thrombosis, deep venous thrombosis, and pulmonary embolism are common and potentially life-, organ-, and limb-threatening vascular diseases. Anticoagulant therapy is recommended in these settings to prevent further thrombosis pending gradual clearance of the thrombotic occlusion by the endogenous fibrinolytic system. Recognition of the importance of the fibrinolytic system in thrombus resolution has resulted in the development of pharmacologic fibrinolytic (thrombolytic) agents to facilitate rapid restoration of vascular patency. Several plasminogen activator (PA) thrombolytic agents with different pharmacokinetic and pharmacodynamic properties have been developed to treat thrombotic disease. Newer PAs have been developed as "fibrin-specific," bolus-administration drugs to primarily treat acute coronary syndromes. Continuous infusions of these fibrin-specific PAs have become popular for the lysis of relatively larger peripheral vascular thromboses. Loss of coveted fibrin specificity due to the generation of fragment X during the continuous infusion of newer tissue-type plasminogen activator–based PAs may result in an increased risk of bleeding, including intracranial hemorrhage. Currently available data fail to provide compelling evidence that newer PAs offer significantly greater efficacy and safety than well-established agents like urokinase when used to treat peripheral vascular thrombosis.
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Arterial and venous thromboembolic events combined, including acute coronary syndromes, stroke, peripheral arterial thrombosis, deep venous thrombosis (DVT), and pulmonary embolism (PE), are likely responsible for more morbidity and mortality than any other condition in the developed world. Coronary artery occlusive disease was responsible for more than 500,000 deaths in the United States alone in 1999 (1 of every 5 total deaths), and it is estimated that 1.1 million Americans will have a new or recurrent myocardial infarction (MI) in 2002.[1] Coronary thrombosis in response to rupture of ather-

osclerotic plaque is the key event in the evolution of stable atherosclerotic coronary artery disease to unstable ischemic syndromes and acute MI.[2]

Acute limb ischemia secondary to peripheral arterial thrombosis and thromboembolism involving native and prosthetic vessels is a relatively uncommon but ominous form of vascular accident. Accurate estimates of acute limb ischemia incidence are lacking due to incomplete data, but national databases suggest a rate of 16 events annually per 100,000 population.[3] Outcomes are inferior if treatment is delayed, and the incidence appears to steadily increase with patient age.[4,5] In a similar fashion to coronary artery thrombosis, acute peripheral arterial thrombosis typically develops at sites of pre-existent atherosclerotic peripheral arterial disease (PAD). PAD has been diagnosed in as many as 17% of men and 20% of women over the age of 55 years and is highly predictive for the co-existence of coronary and cerebral vascular disease.[6] Most patients with PAD are asymptomatic, but the risk of limb loss increases when patients complain of pain at rest or have ischemic ulceration or gangrene.[6] It has been estimated that PAD progresses to critical limb ischemia in 15%–20% of patients.[7] The true incidence of acute limb ischemia is likely proportional to the number of patients with underlying PAD and greater than has been reported to date.

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Acute venous thromboembolic events (VTE), including DVT and PE are common, potentially life-threatening, often preventable vascular conditions associated with trauma, major surgery, advanced congestive heart failure, pregnancy, hormone replacement therapy, malignancy, and inherited hypercoagulability.[8] Proximal lower extremity DVT can result in venous limb gangrene (phlegmasia cerulea dolens), chronic stasis changes related to the post-thrombotic syndrome, and symptomatic PE. Pulmonary embolism in its most severe presentation can result in pulmonary hypertension, right-sided heart failure, cardio-pulmonary collapse, and death.

A common feature of the management of all thromboembolic diseases is the desire to restore vascular patency in a timely fashion to prevent loss of tissue, organ, and limb function, as well as life. Acute arterial thrombosis warrants an attempt at immediate thrombolysis, whereas venous thrombosis only warrants such intervention in extreme cases. This article briefly reviews the pathophysiology of thrombosis, with emphasis on the endogenous fibrinolytic (plasminogen) system, and the pharmacokinetics and pharmacodynamics of established and new pharmacologic thrombolytic agents. Particular attention will be paid to the fibrin specificity of different thrombolytic agents, the association between fragment X generation and bleeding risk, and assessment of optimal clinical strategies for the treatment of peripheral vascular thrombotic occlusions.

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Coronary Thromboses and Peripheral Vascular Thrombotic Occlusions

Structure of Thrombi

The structures of thrombi are heterogeneous and vary somewhat with their location, cause, and age. Components of acute thrombi include fibrin, platelets, erythrocytes, and leukocytes (predominantly polymorphonuclear leukocytes). The local balance between procoagulants and anticoagulants, as well as profibrinolytics and antifibrinolytics, on fibrin and cell surfaces influences thrombus size, stability, and persistence.[9]

Arterial thrombi are platelet rich. It has been demonstrated that rupture of the fibrous cap and exposure of the core of an atherosclerotic lesion are the precipitating events in thrombi formation in coronary arteries.[9] Although fibrinogen is the most important factor in platelet–platelet interactions (ie, platelet aggregation), von Willebrand factor is a crucial participant in platelet adhesion to sites of vascular endothelial damage. The main biological activity of von Willebrand factor is to support platelet adhesion and aggregation in vessels where rapid blood flow (high shear stress) challenges the firm attachment of thrombi to the vascular wall or exposed subendothelial matrix.[10] Furthermore, von Willebrand factor can substitute for fibrinogen in forming the bridge between two platelets, which explains why patients who are deficient in fibrinogen do not demonstrate the degree of platelet dysfunction that might otherwise be expected.

In contrast, venous thrombi are composed predominantly of fibrin and red blood cells, with a variable platelet and leukocyte component. They frequently arise in the peripheral vascular system in large venous sinuses in the calf, in valve cusp pockets either in the deep veins of the calf or thigh, or in venous segments that have sustained direct trauma or extrinsic compression. Venous thrombosis can be produced experimentally by a combination of stasis and systemic hypercoagulability or by stasis and endothelial damage. Natural anticoagulant deficiency, resistance to the anticoagulant effect of activated protein C, and elevated levels of procoagulant proteins are well-defined predispositions to venous thrombosis.[11] Impaired endogenous fibrinolysis appears to be a risk factor for pathologic venous thrombosis formation in certain situations.[12]

The Plasminogen System and Thrombosis

The endogenous fibrinolytic system, also known as the plasminogen system, plays an important role in thrombotic disease (Figure 1). Fibrinolysis is essential for maintaining fluent blood flow, and reduced fibrinolytic activity has been frequently detected in individuals with coronary artery disease and peripheral vascular diseases, as well as those with atherosclerosis risk factors, such as diabetes, hyperlipidemia, and obesity.[13–15] The major reaction of the fibrinolytic system involves the conversion by plasminogen activators (PAs) of the inactive proenzyme, plasminogen, into the active enzyme, plasmin. Plasmin can degrade fibrinogen, fibrin monomers, and cross-linked fibrin (as is found in thrombus) into fibrin(ogen) degradation products (FDPs). These plasmin-mediated reactions generate many species of FDP in common. These reactions also result in unique species of FDP, such as fragment X from fibrinogenolysis and cross-linked FDP (Ddimer) from cross-linked fibrinolysis.[16,17] The plasminogen system plays a key role in limiting the size of hemostatic thrombi, clearing hemostatic thrombi following vascular endothelial injury repair, and preventing pathologic thrombosis.

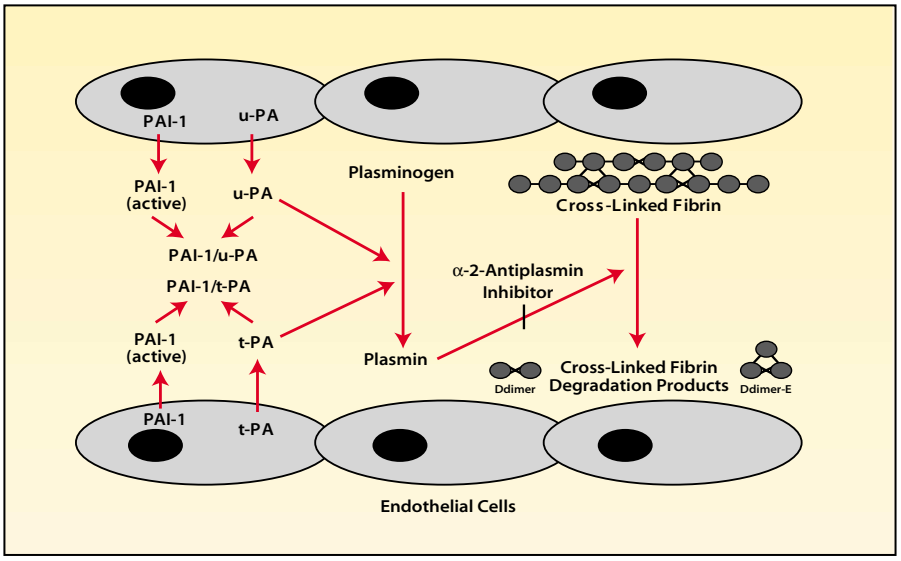

Figure 1. *The endogenous blood fibrinolytic system. Overall regulation of the plasminogen system is mediated by specific molecular interactions between its main components and by the controlled synthesis and release of both plasminogen activators (PAs) and inhibitors (PAIs) from endothelial cells and activated platelets. PAI-1, plasminogen activator inhibitor 1; rt-PA, tissue-type plasminogen activator; u-PA, urokinase-type PA.*

Fibrin(ogen)olytic activity is regulated at the level of the PAs and plasmin itself. Endothelial cell- and platelet-derived plasminogen activator inhibitor-1 (PAI-1) is the major natural inhibitor of the major physiologic PAs, tissue-type PA (t-PA) and urokinase-type PA (u-PA; urokinase). Tissue-type PA is primarily involved in the degradation of fibrin within vascular structures (ie, thrombi), whereas urokinase primarily promotes pericellular proteolytic processes involved in atherosclerosis, macrophage function, ovulation, embryo implantation, wound healing, and tumor metastasis.[16–18] The other major fibrinolytic inhibitor is α-2-antiplasmin, a member of the serine proteinase inhibitor (Serpin) family of proteins, that can neutralize non–fibrin-bound plasmin.[18] The production of these fibrinolytic regulators is modulated by a number of biological factors related to thrombosis and atherosclerosis, including coagulation factors, hormones, growth factors, inflammatory mediators, and lipoproteins.[15]

Thrombolytic Therapy

Early restoration of patency of occluded coronary arteries by thrombolytic therapy has become a routine option in initial therapy for acute MI. Thrombolytic therapy is also used often in the treatment of arterial and venous thromboembolic disease. A wide range of agents is now available for thrombolytic therapy in all of these settings. They are briefly reviewed in the following section.

Plasminogen Activators Used for Treatment of Thrombotic Disease

Recognition of the importance of the endogenous fibrinolytic system in thrombus resolution has resulted in the development of pharmacolog-

Table 1
Properties of Thrombolytic Agents

Thrombolytic Agent	Molecular Weight (kD)	Plasma Half-Life (minutes)	Key Properties
Streptokinase	48,000	16/90	Complexes with plasmin(ogen) to gain activity
Urokinase	32,000/54,000	14	Direct plasminogen activator
r-Urokinase*	54,000	7	Recombinant high-molecular weight urokinase
r-Prourokinase*	49,000	7	Little intrinsic activity, converted to urokinase
rt-PA	68,000	3.5	Exhibits great degree of fibrin affinity and specificity
APSAC*	131,000	40–90	Complex of streptokinase with plasminogen
TNK-rt-PA	65,000	15	A modified rt-PA with a longer half-life, greater fibrin specificity and greater resistance to PAI-1
Reteplase	39,000	14	A truncated rt-PA with a longer half-life
Alteplase	70,000	4–8	A recombinant rt-PA
Monteplase*	68,000	23	Mutant of rt-PA
Lanoteplase*	53,500	23–37	Deletion mutant of rt-PA with prolonged half-life
Pamiteplase*	–	30–47	Modified rt-PA with deletion of the kringle 1 domain
Staphylokinase*	16,500	6	PA produced by *Staphylococcus aureus*

r-Urokinase, recombinant urokinase; r-Prourokinase, recombinant prourokinase; rt-PA, recombinant tissue-type plasminogen activator; APSAC, anisoylated plasminogen streptokinase activator complex; PAI-1, plasminogen activator inhibitor 1.
Data from Bell,[19] Ouriel,[20] and Verstraete.[21]
*Not commercially available.

ic fibrinolytic (thrombolytic) agents to facilitate rapid restoration of vascular patency. Currently available PAs and their key characteristics are summarized in articles by Drs. Bell and Ouriel in this supplement and in Table 1.[19–21]

Most thrombolytic agents are PAs fashioned after endogenous rt-PA or urokinase. Traditional thrombolytic drugs include bacteria-derived streptokinase, anisoylated plasminogen streptokinase activator complex (APSAC), urokinase (two-chain u-PA), and recombinant rt-PA (rt-PA). Newer molecules have been and are being developed in an attempt to improve on the traditional agents. Major goals of new thrombolytic agent development include increasing fibrin specificity to theoretically reduce bleeding complications, prolonging initial plasma half-life to facilitate single- or double-bolus administration, and reducing sensitivity to inactivation by PAI-1.

New thrombolytic agents include mutants of PAs, chimeric PAs, conjugates of PAs with monoclonal antibodies, and novel PAs from animal or bacterial origin. Recombinant rt-PA has provided some evidence of clinical superiority over other first-generation fibrinolytic agents (streptokinase, urokinase, APSAC),[22] but these findings are controversial (see next page). Monteplase is a modified rt-PA constructed by substituting a single amino acid in the epidermal growth factor domain. It has a prolonged half-life of more than 20 minutes, as compared with 4 minutes for native rt-PA. TNK-rt-PA differs from rt-PA by three sets of mutations. The Asn^{117}→Gln and Thr^{103}→Asn mutations promote a lower plasma clearance rate and greater fibrin specificity. The Lys^{296}-His^{297}-Arg^{298}-Arg^{299}→Ala-Ala-Ala-Ala mutation imparts an 80-fold increased resistance to PAI-1.[23] Reteplase is a nonglycosylated deletion mutant of wild-type human rt-PA composed of only the kringle 2 and the protease domains of the parent molecule. Lack of the finger domain imparts lower fibrin binding affinity. Lack of glycosylation, a finger domain, and epidermal growth-factor domain imparts an extended half-life.[24] Lanoteplase is a deletion mutant of rt-PA with a half-life that is about 10 times longer than alteplase, making it suitable for single-bolus injection. YM866 is another mutant of rt-PA, in which the amino acids 92–173 of kringle 1 were deleted and arginine 275 replaced by glutamic acid. The changes extended the half-life for the altered molecule. Recombinant glycosylated pro-urokinase has a greater stability than recombinant unglycosylated pro-urokinase and is rapid acting and safe in the clinical doses used.[25] Staphylokinase is produced by *Staphylococcus aureus*. It appears to have substantial thrombolytic activity, but it may also be immuno-

genic.[21] Vampire bat (Desmodus rotundus) salivary PA possesses 85% primary structure homology to human rt-PA but lacks a kringle 2 domain.

Bleeding Risk Associated with Thrombolytic Therapy

Bleeding is the most common complication associated with thrombolytic therapy. The bleeding stems from plasmin's inability to differentiate between hemostatic and pathologic thrombi. This complication can range from minor bleeding from an intravenous infusion site to life-threatening hemorrhage.[26] Intracranial hemorrhage (ICH) is a relatively uncommon but serious complication of thrombolysis. The incidence of ICH associated with thrombolysis for peripheral vascular disease is less well-defined.

The factors that increase risk for bleeding during thrombolytic therapy are not fully understood. However, Gurwitz and associates[27] used the National Registry for Myocardial Infarction to determine risk factors for this adverse event in individuals treated with rt-PA for MI. Their analysis of 673 patients with ICH indicated that older age, female sex, black ethnicity, systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 100 mm Hg, history of stroke, rt-PA dose > 1.5 mg/kg, and lower body weight were all significantly associated with increased risk for ICH. It is also possible that the properties of the agent used for thrombolysis may contribute to the risk for bleeding complications. This issue is addressed in the following section.

Gurwitz and associates found that older age, female sex, black ethnicity, systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 100 mm Hg, history of stroke, rt-PA dose > 1.5 mg/kg, and lower body weight were all significantly associated with increased risk for intracranial hemorrhage.

Table 2
Fibrin Specificity of Different Thrombolytic Agents

Thrombolytic Agent	Fibrin Specificity
Streptokinase	Low
Urokinase	Low
r-Urokinase	High
r-Prourokinase*	High
rt-PA	High
APSAC*	Very high
TNK-rt-PA	Very high
Reteplase	Moderate
Altepase	High
Monteplase*	High
Lanoteplase	Moderate
Pamiteplase*	High
Staphylokinase*	Extremely high

r-Prourokinase, recombinant prourokinase; rt-PA, recombinant tissue-type plasminogen activator; APSAC, anisoylated plasminogen streptokinase activator complex.
Data from Ouriel[20] and Verstraete.[21]
*Not commercially available.

Fibrin specificity of thrombolytic agents and risk for hemorrhagic complications of therapy. Thrombolytic agents can be characterized along a variety of dimensions,[20] but one that is often used is fibrin specificity (Table 2). The ability of a thrombolytic agent (PA) to distinguish between plasminogen in the general circulation and plasminogen bound to fibrin surfaces dictates its fibrin specificity. Activation of fibrin-bound plasminogen results in the generation of fibrin-bound plasmin that is protected from inactivation by α-2-antiplasmin. Bound plasmin generates soluble fibrin degradation products, whereas circulating plasmin degrades fibrinogen into FDPs. Fibrin specificity differs from fibrin affinity, which is a measure of how avidly a given agent binds to fibrin but not its specificity for this molecule.[20] At present, there is little evidence to support the view that differences in fibrin affinity among PAs are significantly correlated with either the efficacy or safety of these preparations.[28,29] High fibrin specificity is thought to be associated with lower risk for hemorrhagic complications in patients undergoing thrombolytic therapy because of the belief that plasmin born on the fibrin surface of a thrombus will restrict its activity only to that surface. This view is not universally supported by available data from large-scale clinical trials nor has it been borne out in clinical practice.

The relationship between high fibrin specificity and reduced bleed-

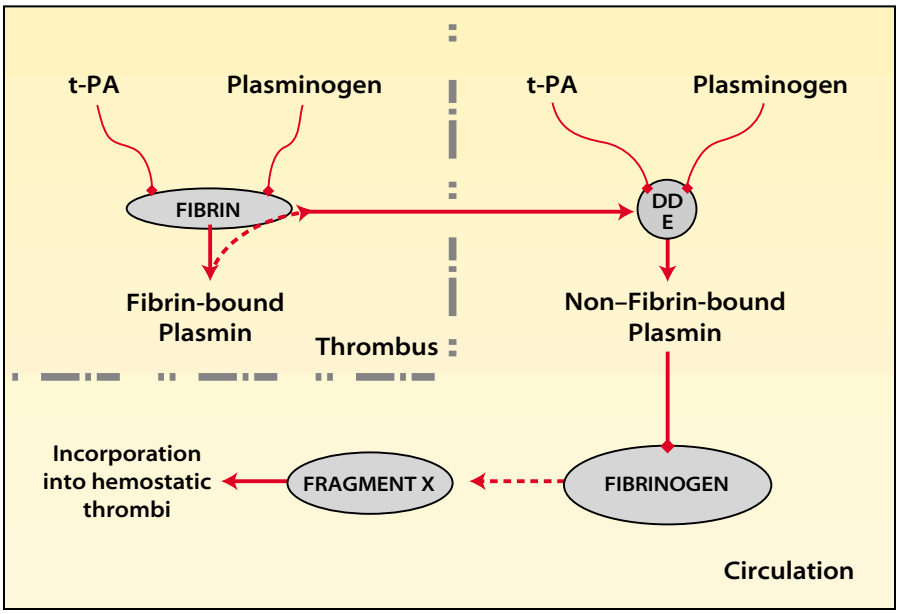

Figure 2. *Mechanism by which kringle 2–containing, "fibrin-specific" plasminogen activators like rt-PA can lose their fibrin specificity and generate circulating plasmin activity and resultant fragment X.*

ing risk is supported by the results of a recent study. The results of the Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT)-2 trial,[30] which included 16,949 patients with acute MI, showed that the use of a highly fibrin-specific thrombolytic agent, TNK-rt-PA, compared with rt-PA, was associated with a significantly lower risk for major noncerebral bleeding. This lower rate of bleeding complications was correlated with a significant reduction in the need for blood transfusions. The ASSENT-2 investigators also reported that TNK-rt-PA was associated with a significantly lower risk for all noncerebral bleeding than the less-specific agent alteplase.[31] Intracranial bleeding rates were comparable with the two agents.

Results from other large-scale studies support the opposing view that high fibrin specificity may actually be associated with increased risk for intracranial bleeding in patients undergoing thrombolytic therapy for acute MI. For example, the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial showed that the risk of intracranial bleeding was slightly higher in 41,021 patients with MIs who received treatment with rt-PA as compared with streptokinase.[32] These findings are consistent with those from another very large-scale comparison of streptokinase with rt-PA in 20,768 patients with MI (Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico 2; GISSI-2), which showed a significantly higher risk of stroke in patients who received the latter, more fibrin-specific agent.[33] Similarly, the Third International Study of Infarct Survival (ISIS-3) showed that treatment of patients with APSAC was associated with increased risk for intracranial bleeding compared with streptokinase in a large cohort of 41,299 patients who received thrombolytic therapy for suspected MI.[34]

There are a number of potential explanations for the association between high fibrin specificity and increased intracranial bleeding observed in the patients treated in the GUSTO, GISSI-2, and ISIS-3 trials. These include the inability of fibrin-specific agents to distinguish between pathologic thrombi and hemostatic thrombi and the possibility that treatment with fibrin-specific agents resulted in greater degradation of hemostatic fibrinogen and other circulating coagulation factors than streptokinase. Finally, it may be that fibrin-specific therapy resulted in increased production and accumulation of fragment X and that this elevated bleeding risk. This possibility is discussed in detail in the following section.

Fragment X and bleeding risk. PAs once believed to be safer because of their fibrin-specificity may actually result in greater bleeding risk by virtue of their generation and accumulation of the fibrin degradation product (DD)E and fragment X. (DD)E is a cross-linked fibrin degradation product that can bind both plasminogen and rt-PA and protect bound plasmin from α-2-antiplasmin.[35] Fragment X is a high-molecular-weight, "clottable" fibrinogen degradation product that, when incorporated into a forming thrombus, makes a thrombus more readily lysed.[36] The sequence of molecular events that can lead to a loss of rt-PA fibrin-specificity include the following: 1) rt-PA and plasminogen bind to a fibrin surface on a pathologic thrombus, resulting in the generation of fibrin-bound plasmin; 2) fibrin-bound plasmin degrades the thrombus, resulting in the formation of fibrin degradation products like (DD)E; 3) other rt-PA (via their kringle 2 domains) and plasminogen molecules bind to circulating (DD)E and generate fibrin- and non–fibrin-bound plasmin in the circulation far from the target thrombus; and 4) the circulating plasmin activity

degrades circulating fibrinogen and leads to the production and accumulation of fragment X. Hypofibrinogenemia ensues and hemostatic thrombi that have incorporated fragment X become prone to rapid lysis by circulating and bound plasmin.[37] (See Figure 2).

Fragment X persists in the circulation for as long as 24 hours after an infusion of rt-PA to patients with acute coronary thrombosis. Similar patients given streptokinase have lower circulating levels of fragment X and higher concentrations of smaller degradation products, such as fragment D and fragment E, in their circulation. Bolus administrations of rt-PA may result in less fragment X production than infusions over several hours. When added to the plasma of healthy dogs, fragment X results in significant lengthening of the thrombin time, and this effect is thought to be due to competition between fragment X and fibrinogen for the fibrinogen binding sites on thrombin.[38]

Optimal Thrombolytic Therapy for Peripheral Vascular Thrombotic Occlusions

Several recent reviews have summarized results from studies that have compared the safety and efficacy of different fibrin-specific PAs employed for thrombolysis in coronary arteries of patients with MIs, but there is less information about the use of different agents for peripheral vascular clot lysis. The most important available data are reviewed in the following section.

Treatment of Peripheral Arterial Thromboembolism

The management of acute limb ischemia includes rapid clinical assessment, prompt initiation of anticoagulation to reduce or prevent thrombus propagation and provide protection against further embolization, pain control, and rapid initiation of therapy to re-establish perfusion of the affected limb. The results of several large-scale trials have documented the effectiveness of thrombolytic therapy with a number of different agents in patients with peripheral arterial thromboembolism.[39,40] Unlike in acute MI, where intravenous bolus fibrin-specific PA dosing is necessary to rapidly achieve high concentrations of plasmin activity at the site of thrombosis and facilitate rapid lysis of a relatively small thrombus, lysis of larger-diameter and longer peripheral thromboses is best achieved with catheter-directed infusions of fibrin-specific PA over several hours to days. Drugs designed for bolus or brief infusion administration to treat acute coronary thrombosis may be associated with an excessive bleeding risk when given by extended continuous infusion. Such infusions may foster the loss of "fibrin-specificity" described above, accumulation of fragment X, and increased rates of bleeding.

Bleeding complications occurred significantly less often in patients treated with urokinase, and cardiopulmonary complications necessitating transfer to the intensive care unit occurred significantly more frequently in the patients treated with rt-PA.

However, there have been few head-to-head comparisons of different preparations. Ouriel and associates[41] reported data for 653 consecutive patients who were treated for lower extremity occlusions (mainly arterial) with catheter-directed urokinase, rt-PA, or both agents. Bleeding complications occurred significantly less often in the patients treated

Main Points

- The endogenous fibrinolytic system plays a key role in limiting the size of hemostatic thrombi, clearing hemostatic thrombi following vascular endothelial injury repair, and preventing pathologic thrombosis; the biologically active product of the fibrinolytic system is the enzyme plasmin, which degrades fibrin.
- Plasminogen activators once believed to be safer because of their fibrin-specificity may actually result in greater bleeding risk by virtue of their generation of the fibrin degradation product (DD)E and fragment X.
- A relationship between high fibrin specificity and reduced bleeding risk is supported by the results of the ASSENT-2 trial; however, the GUSTO, GISSI-2, and ISIS-3 trials support the opposing view that high fibrin specificity may actually be associated with increased risk for intracranial bleeding in patients undergoing thrombolytic therapy.
- Studies comparing urokinase to recombinant tissue-type PA (rt-PA) for the treatment of peripheral arterial thrombosis and deep venous thrombosis have found, at times, significant trend toward more frequent bleeding complications with rt-PA.

with urokinase, and cardiopulmonary complications necessitating transfer to the intensive care unit occurred significantly more frequently in the patients treated with rt-PA.

Meyerovitz and associates[42] carried out a randomized prospective trial to compare intra-arterial rt-PA with urokinase in 32 patients with peripheral arterial or bypass graft occlusions. Clot lysis occurred significantly more rapidly with rt-PA than with urokinase, but there was a trend toward more frequent bleeding complications in the patients who received the former agent. There was no between-treatment difference in 30-day clinical success.

Treatment of Deep Vein Thrombosis

Thrombolytic therapy may be highly effective for the treatment of patients with acute DVT, and such treatment has several potential benefits in this setting: 1) it can restore venous flow; 2) it may preserve or restore venous valvular function; and 3) it may reduce the risk for long-term complications and chronic symptoms related to the postthrombotic syndrome.[43,44]

Schweizer and associates have carried out two studies that compared urokinase with rt-PA for the treatment of patients with DVT.[45,46] The first trial included 69 patients, and results showed that urokinase was more effective than rt-PA in achieving complete lysis (50% vs 27%) and in reducing the incidence of serious postthrombotic complications (41% vs 68%).[45] Results from the second, larger study of 250 patients with acute DVT indicated treatment with rt-PA was associated with a higher risk for bleeding complications than urokinase.[46]

Summary

Increased understanding of the molecular biology of the coagulation and fibrinolytic cascades has resulted in the development of new and effective therapies for arterial and venous thrombotic disease. The results briefly summarized in this review support the effectiveness of thrombolytic therapy for both acute and chronic arterial occlusion, as well as VTE. However, currently available clinical results provide no compelling evidence that new preparations with improved pharmacokinetic properties and/or high fibrin specificity offer significantly greater efficacy or safety than established agents (eg, urokinase) for the treatment of peripheral arterial occlusion or DVT. Moreover, safety data from large-scale studies of patients who received thrombolytic therapy subsequent to MI indicate that newer agents with high fibrin-specificity may be associated with an increased risk for intracranial bleeding, possibly associated with the development of high plasma concentrations of fragment X. Clearly, results from more well-designed, prospective clinical trials are needed to determine whether fibrin-specific over nonfibrin-specific agents and novel means of thrombus dissolution offer significant advantages over established PAs in the treatment of thromboembolic disease. ■

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