Therapeutic Agents—Pharmacokinetics and Pharmacodynamics

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Various thrombolytic agents have been studied as activators of the plasminogen-plasmin system for thrombolysis of thrombus formation. They include streptokinase, urokinase, tissue plasminogen activators, single-chain urokinase plasminogen activator, and anisoylated or acylated plasminogen-streptokinase activator complex (APSAC), only some of which are commercially available. All thrombolytic agents, including APSAC (not commercially available), recombinant tissue plasminogen activator, and prourokinase, generate great quantities of degradation products of fibrinogen or fibrin. All of the second-generation thrombolytic agents induce systemic activation of the entire fibrinolytic system, and none are capable of specifically activating the fibrinolytic system at the site of thrombus formation. The most systemically active agent known at the present time is APSAC. Trials show that bleeding occurs as frequently with the second-generation agents as with the older agents, and further studies may even find that the newer agents are associated with more bleeding than urokinase and streptokinase have been. With knowledge of the properties of the various thrombolytic agents available today, the physician can intelligently select the optimal agent for a given patient problem.

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This article will review the pharmacokinetics and pharmacodynamics of various thrombolytic agents.

Thrombolytic Agents

Streptokinase

The therapeutic utilization and enhancement of the fibrinolytic system was made possible in 1933 by Tillet and Garner,[1] who first described the exogenous plasminogen activator isolated from β-hemolytic streptococci. This activator was subsequently named "streptokinase" by Christensen and MacLeod in 1945,[2]

and was found to react stoichiometrically with human plasminogen by Ratnoff in 1948.[3] Further work by Sherry and colleagues[4,5] and Johnson and McCarty[6] resulted in the introduction of streptokinase for thrombolysis of endogenous thrombus formation.

Streptokinase is a single-chain glycoprotein with a molecular weight of 45,000–50,000 daltons and a very low, < 10% carbohydrate content.[7,8] A primary structure determination reveals isoleucine at the amino-terminus, lysine at the carboxyl-terminus, and the absence of any intra-chain disulfide bridges.[9] The secondary structure is mainly random coil with only about 10% α-helix.[7,8] Streptokinase has one major isoelectric point at pH 4.0.[6,10]

Unlike the other known activators of the plasminogen-plasmin system, streptokinase is not an enzyme. Streptokinase within the streptokinase-plasminogen complex is transformed into activated plasminogen possessing a proteolytic active serine site.[11,12] The streptokinase-plasminogen activator complex is then able to cleave the Arg_{560}-Val_{561} "activator bond," converting both complexed and free plasminogen to plasmin. The streptokinase-plasmin complex thus formed also acts as an activator.[13,14]

While plasminogen is being converted to plasmin, the streptokinase molecule within the activator complex undergoes proteolytic degradation. Streptokinase fragments ranging from 40,000–10,000 daltons are formed,[15,16] all of which retain some degree of activator activity.[17]

Streptokinase interacts with various forms of the plasmin(ogen) molecule, including Glu-plasminogen, Lys_{77}-plasminogen, Val_{442}-plasminogen, and the β-chain of plasmin.[18] In vitro studies show that the activity of the activator complex varies with both the size of the streptokinase fragment and the form of plasmin(ogen) within the complex.[19–22] The amount of activator activity is proportional to the size of the streptokinase fragment and inversely proportional to the form of plasmin(ogen), with the streptokinase–β-chain complex having the highest degree of activator activity.

In vivo, the situation is more complex. The binding of the fibrinogen degradation-product fragments Y and E to plasminogen enhances the interaction with streptokinase.[23] In addition, the binding of plasminogen to streptokinase prevents inhibition by α-2-antiplasmin than plasmin itself.[23]

Because streptokinase is not naturally occuring in the human body, it is antigenic and can induce the production of antistreptokinase antibodies. The metabolism and excretion of streptokinase are unclear, because the clearance rate of streptokinase depends on the availability of plasminogen substrate. In the human body two half-lives have been identified.[24] The first half-life is 18 minutes and represents clearance after binding with antibodies or inhibitors (represents about 80%–85% of a single dose given intravenously), and a second half-life is approximately 83 minutes (represents about 10%–15% of an administered dose).

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Urokinase

In the 1950s, severe febrile reactions associated with streptokinase prompted the search for another thrombolytic agent. Human urine was known to contain a fibrinolytic agent.[25] This agent was identified as a plasminogen activator by Williams in 1951,[26] was subsequently named "urokinase" by Sobel in 1952,[27] and was made by Plough and Kjeldgaard[28] and Lesuk and colleagues.[29] Detailed studies by Sherry and coworkers[4,30] on the physicochemical properties of urokinase implemented its introduction for therapeutic thrombolysis.

Purification of urokinase, the first tissue (from renal parenchymal cells) plasminogen activating agent, has revealed several forms of varying molecular weights.[29,31] The two major species are a form with a 54,000-dalton high molecular weight (HMW) and a form with a 33,000-dalton low molecular weight (LMW), both having similar plasminogen activator activity.[32] The HMW form is the native form of the molecule and is probably degraded to the LMW form through limited proteolysis by either autodigestion or other proteases found in the urine.[33,34]

HMW urokinase is a glycoprotein consisting of two polypeptide chains (33,000 and 54,000 daltons) connected by disulfide bonds.[35,36] The molecule contains 6% carbohydrate, mainly mannose, N-acetylglucosamine, and N-acetyl neuraminic acid.[37] The 33,000-dalton chain contains the serine active site.[38,39] There is one major isoelectric form of HMW urokinase at pH 8.6 and three LMW forms at pH 8.35, 8.6, and 8.7.[40]

Urokinase is a serine protease[41] and hydrolyzes synthetic esters containing arginine and lysine.[42] Unlike streptokinase, urokinase directly activates plasminogen by cleaving the Arg_{560}-Val_{561} "activation bond."

Although kinetic data comparing the two forms of urokinase are

essentially the same,[22] the HMW form appears to have a greater thrombolytic effect.[41]

Urokinase is distinguished from an extrinsic plasminogen activator both immunochemically[43–46] and by its ability to bind to fibrin.[47–49] The ability of human kidney cells in tissue culture to produce urokinase[50,51] indicates that urokinase is probably synthesized by the kidney. Plasminogen activators immunochemically identical to urokinase, however, have also been isolated from normal heart tissue[52] and from human plasma,[53–56] as well as from several human malignant neoplasms grown in tissue culture, including those from the ovary,[56] pancreas,[57] lung,[58] and breast.[59] The plasma half-life of urokinase is approximately 15 minutes.[24]

Because normal human urine contains only a small amount of urokinase (a few micrograms per milliliter), about 1500 liters of human urine are required to produce enough urokinase for a single thrombolytic treatment for one patient.[55] Fortunately, methods of producing urokinase from human neonatal kidney-cell culture have been developed.[50,60] Both urinary (ex-U.S.) and tissue-culture urokinase (U.S.) are available for clinical use and are biochemically similar in producing a fibrinolytic state.[61]

Tissue Plasminogen Activators

Human tissue plasminogen activators (rt-PA) are endogenously synthesized and secreted by vascular endothelial cells as a glycosylated protein of 68,000 daltons and under the regulation of a gene located on chromosome 8. As it is released by the endothelial cell, rt-PA is 562 amino acids in a single chain and organized into five discrete domains linked in various locations by 17 disulfide bridges initiated by an amino terminal and ending with a carboxy terminal.[62] From the amino terminal inward residues 4 to 50 possess the homology of fibronectin; this is called the "finger" domain. Residues 51 to 87 share a homology with the precursor of epidermal growth factor also found in urokinase, protein C, coagulation Factors IX and X, and the receptor for low-density lipoprotein. Residues 88 to 175 and 176 to 263 form two sequential kringle domains. Each of these domains are also found with three disulfide linkages. These domains are also found in urokinase, prourokinase, prothrombin, and plasminogen. From residues 264 to 562 is the catalytic portion of the molecule containing the triad of histidine, asparagine, and serine. The recombinant molecule (rt-PA) employed therapeutically is 527 amino acids in length and is morphologically different from the naturally occurring molecule with respect to the spatial arrangement of the kringle domains. Binding of the rt-PA to fibrin in vitro is mediated via the finger and 2nd kringle domains. Activation of the rt-PA molecule takes place when Arg_{275}-Ile_{276} is cleaved. Once activated, it now can activate its substrate plasminogen at the identical site acted upon by streptokinase and urokinase.

Prourokinase —Single-Chain Urokinase Plasminogen Activator

Prourokinase (r-pro-UK, not commercially available) is a single-chain precursor of urokinase secreted by the human kidney, lung, and other cells. The proenzyme is converted into two-chain urokinase by limited hydrolysis by plasmin or kallikrein at the Lys_{158}-Ile_{159} cleavage site. The r-pro-UK zymogen is composed of 411 amino acids with a molecular mass of 54 kd. Human recombinant glycosylated prourokinase (r-pro-UK) (not commercially available) is produced by a recombinant technology in which the human r-pro-UK gene is expressed in a mouse myeloma cell line. r-proUK is glycosylated and is greater than a 99% single-chain zymogen form. The protein behaves in the same manner as natural nonrecombinant r-pro-UK obtained from tissue culture. The covalently attached oligosaccharide contributes approximately 5%–6% to the mass. The r-pro-UK is cleared from the circulation, with more than 50% removed within 8–10 minutes in mammals.[63] This agent is converted to the two-chain active form before it is cleared by the liver, where it is rapidly inactivated and catabolized into amino acids.

Pro-UK functions as a potent plasminogen activator of fibrin-bound plasminogen without requiring extensive systemic conversion to two-chain UK. Thus, the entire thrombolytic process is confined to the fibrin clot itself.

In the presence of insoluble fibrin, r-pro-UK functions as a potent plasminogen activator of fibrin-bound plasminogen without requiring extensive systemic conversion to two-chain urokinase.[64,65] Thus, the entire thrombolytic process is confined to the fibrin clot itself, providing the fibrin specificity of r-pro-UK without direct fibrin binding.[66]

Recombinant Urokinase

Recombinant urokinase (r-UK, not commercially available) is a 253 amino-acid–containing structure that is secreted in vitro by SP2/0 cells as a

Table 1
Properties of Thrombolytic Agents

	SK	UK	rt-PA	APSAC	Plasminogen
Source	Streptococcal culture	Human neonatal kidney cell tissue culture	Heterologous mammalian tissue culture	Streptococcal culture	Human hepatocytes
Molecular weight	47,000	32,000–54,000	70,000	131,000	92,000
Type of agent	Bacterial proactivator	Tissue plasminogen activator	Tissue plasminogen activator	Bacterial proactivator	Plasma substrate
Plasma clearance (min)	12–18	15–20	2–6	40–60	53 (hr)
Fibrinolytic activation	Systemic	Systemic	Systemic	Systemic	_
Fibrin binding	Minimal	Moderate	High	Minimal	_
Antigenic	Yes	No	No	Yes	_
Allergic reactions	Yes	No	No	Yes	–
Gene (Kb)	–	6.4	36.6	–	30
Chromosome location	–	10	8	–	6

SK, streptokinase; UK, urokinase; rt-PA, recombinant tissue plasminogen activator; APSAC, anisoylated (acylated) plasminogen streptokinase activator complex.

single-chain structure. The zymogen, when treated with immobilized plasmin, completely converts pro-urokinase to an active two-chain form (r-UK) by the hydrolysis of a Lys_{158}-Ile_{159} amide bond. Recombinant urokinase shares many common structural elements with naturally occurring HMW, 50,000- to 60,000-dalton urokinase. The α-chain is composed of the growth-factor region, residues 9 to 45, the kringle domain, residues 46 to 134, and the connecting peptide sequence, residues 135 to 158. The β-chain residues 141 to 159 contain the critical residues of the catalytic triad His_{204}, Asn_{255}, and Ser_{356}. The presence of carbohydrate in r-UK appears to have an influence on the catalytic activity of the molecule. The rate of plasminogen activation is greatest with nonglycosylated molecules. The rapid onset of the generation of plasmin by glycosylated r-UK may be reduced, and the overall stability of this molecule and its persistent activity in plasma may have a considerable advantage in thrombus lysis and the maintenance of vessel patency.

Anisoylated Plasminogen-Streptokinase Activator Complex

P-anisoylated or acylated Lys–plasminogen-streptokinase activator complex (anistreplase, Eminase, not commercially available) is a 1:1 stoichiometric inert complex of streptokinase with plasminogen in which the active serine center is protected by a p-anisoyl (acyl) group placed directly on serine 740 of the plasminogen molecule. The acylation process is performed with a methodology so as not to alter or disturb the five convex discoid kringle structures on the opposite side of the molecule.[67] These five kringle structures are critical because they possess the high-affinity lysine binding sites necessary for the binding of this compound to fibrin strands. When this anisoylated plasminogen streptokinase activator complex (APSAC) with a molecular weight of 131,000 daltons is placed in an aqueous phase, deacylation occurs by simple ester hydrolysis that follows pseudo–first-order kinetics in a temperature-dependent manner. Products of the deacylation reaction are p-anisic acid and the free Lys-plasminogen-streptokinase complex in equimolar quantities. Deacylation occurs at approximately equal rates in the free plasma and when bound to a fibrin clot. The free activator complex displays potent enzymatic activity in prompting the formation of the active fibrinolytic enzyme plasmin form of its proenzyme plasminogen. The biologic half-life in the circulation varies between 40–90 minutes, and some metabolites may

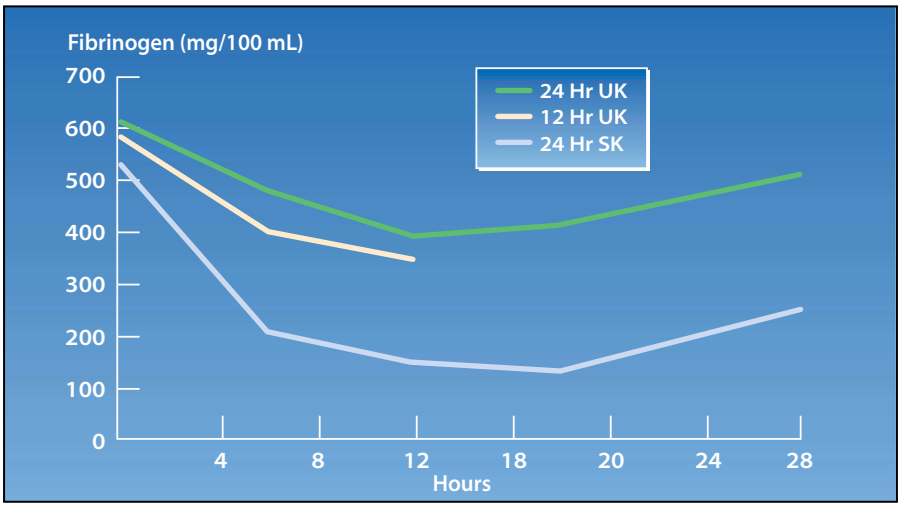


Figure 1. *Mean plasma fibrinogen concentrations following infusions of urokinase (UK) and streptokinase (SK). Data from Bell WR. Thrombolytic therapy: a comparison between urokinase and streptokinase: from a national cooperative study.* Semin Thromb Hemost. *1975;2:1–13.*

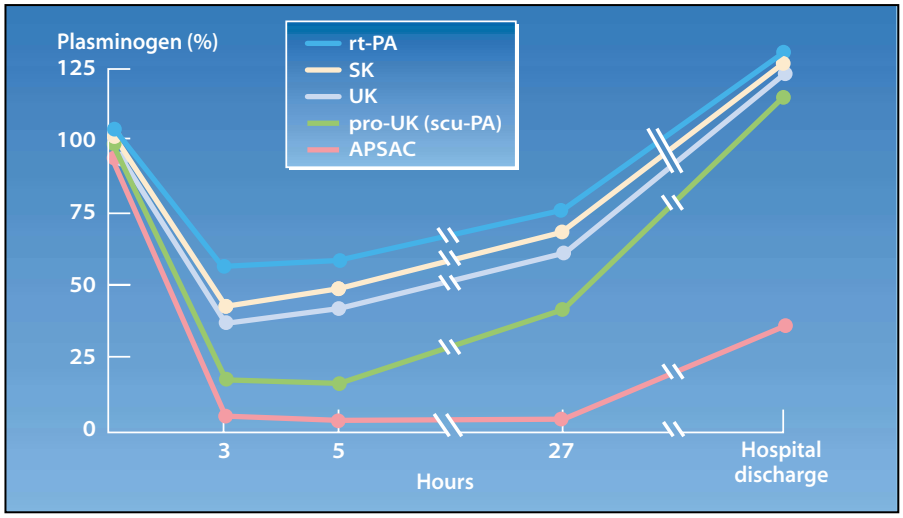
be present for close to 24 hours. The biologic activity of APSAC is expressed in units and selected in a manner where 1 mg of the compound equals 1 unit. The commonly employed clinical dose of 30 units of APSAC approximates 1.1 million units of streptokinase.[68,69] The properties of the commercially available thrombolytic agents are listed in Table 1.

First Generation Thrombolytic Agents

When the first-generation thrombolytic agents urokinase and streptokinase are administered in the standard doses universally employed to treat pulmonary emboli, deep vein thrombosis (spontaneous or catheter-associated), arterial thrombosis or emboli, or acute myocardial infarction, and measurements are made of various circulating plasma proteins before infusion of the agent, at various times during the infusion, and again following discontinuation of the agent, plasma fibrinogen progressively declines from time zero, undergoing degradation by generated plasmin, to reach nadir low values at between 5 to 7 hours (lower values with streptokinase than those observed with urokinase) at 100 mg/dL ± 30 mg/dL (mean values). These values remain low for the duration of the infusion; then following discontinuation of the infusion they progressively increase. Between 36–48 hours after discontinuation, the fibrinogen levels are back to baseline normal concentrations. Both urokinase and streptokinase in the active forms have only a very minimal and limited capacity to alter fibrinogen in the absence of plasminogen. These agents have almost no affect on plasminogen-free fibrinogen. The degradation products resulting from the lysis of fibrinogen or fibrin actually have the capacity to stimulate the hepatocyte to synthesize fibrinogen. Thus, even during the last 6–8 hours of the infusion of the thrombolytic agent a slight to modest increase in plasma fibrinogen concentration can be observed (Figure 1).

Similarly, plasma-plasminogen progressively declines in concentration following the institution of streptokinase and urokinase. This decline is directly related to the conversion of the inert prozyme plasminogen that circulates in the euglobulin fraction of the blood to the potent, nonspecific, proteolytic enzyme plasmin. The concentration of plasma-plasminogen is considerably lower when streptokinase or any streptokinase-containing compound is being given (because streptokinase must form a 1:1 stoichiometric com-

Figure 2. *Comparison of changes in mean plasminogen concentrations after infusions of recombinant tissue plasminogen activator (rt-PA), streptokinase (SK), urokinase (UK), prourokinase (pro-UK) single-chain urokinase plasminogen activator (scu-PA), and anisoylated (acylated) plasminogen streptokinase activator complex (APSAC). Data from Rao et al.*[73]



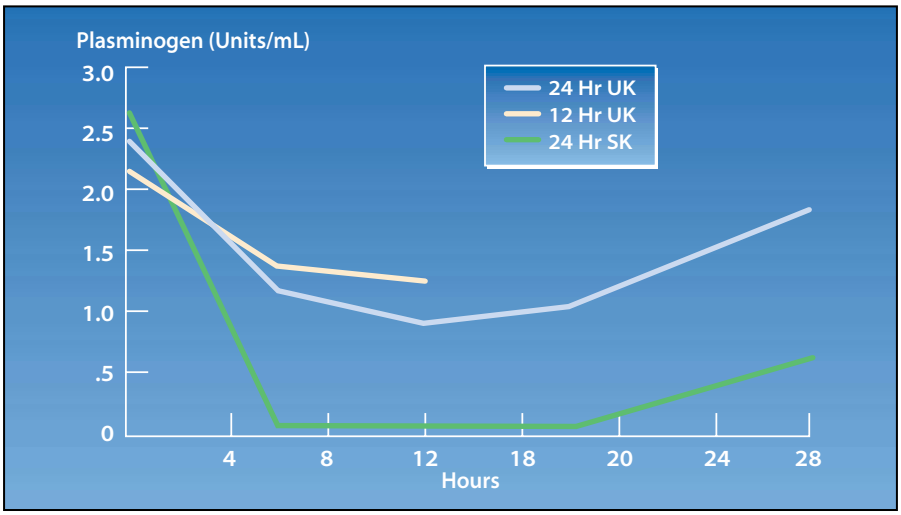


Figure 3. *Mean plasma plasminogen concentrations following infusions of urokinase (UK) and streptokinase (SK). Data from Bell WR. Thrombolytic therapy: a comparison between urokinase and streptokinase: from a national cooperative study.* Semin Thromb Hemost. *1975;2:1–13.*

plex with plasminogen before it has the property to convert plasminogen to plasmin). Thus, in facilitating the streptokinase-plasminogen complex, the plasma-plasminogen complex promotes plasminogen to plasmin, and the plasminogen concentration is further reduced. When employing streptokinase, one must be cautious so as not to deplete the circulating blood of plasminogen, because if this occurs there will not be sufficient plasminogen from which to generate plasmin. Such a state may indeed lead to the induction of thrombus formation (Figure 2).

The degradation products of fibrinogen or fibrin (FDP-fdp) are the absolute index to the activity of the fibrinolytic system in humans. The only known pathway by which the FDP-fdp are present in circulating blood is via the fibrinolytic system in man. These degradation products result from the digestion of fibrinogen and/or fibrin by plasmin. Thus, when these FDP-fdp reach excessive quantities in the circulating blood, they are easily detected and unequivocally establish intense activation on a systemic level of the plasminogen-plasmin proteolytic enzyme system. When both streptokinase and urokinase are administered in the standard doses, large quantities of FDP-fdp are detected. The quantity detected associated with streptokinase, however, is considerably greater than that observed when urokinase is administered (Figure 3). These data concerning the alterations in fibrinogen, plasminogen, and FDP-fdp observed in the circulating blood following the administration of streptokinase and urokinase unequivocally establish the presence of systemic activation of the fibrinolytic system.

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Second-Generation Thrombolytic Agents

Because there was thought to be an association between systemic activation of the fibrinolytic system and bleeding observed during treatment with thrombolytic therapy, emphasis was placed on the identification or design of agents that would activate the fibrinolytic system locally at the site of thrombus formation and therefore not give rise to systemic activation of the fibrinolytic system. As a result of considerable work, a second generation of thrombolytic agents became available which included the following:

- Recombinant tissue plasminogen activators (rt-PA, r-PA, TNK)
- Anisoylated (acylated) plasminogen streptokinase activator complex (APSAC)
- Prourokinase (r-pro-UK) single-chain urokinase plasminogen activator (scu-PA)

However, to prepare the monospecific antibody against human fibrin, a nonhuman species or a nonhuman cell line must be employed to generate the antibody (IgG). Thus, this foreign IgG, when placed inside the human body, is capable of acting as an antigen and giving rise to an antibody. The antibody produced is a Class I antibody that induces complement-binding, anaphylactic antigen-antibody interactions, and resultant immune complexes in the circulating blood. For these reasons, these antibody-

directed thrombolytic agents cannot be employed in humans at present.

In view of the availability of rt-PA, APSAC, and r-pro-UK, however, various questions about their characteristics arise: Are these second-generation agents as capable as initially designed and advertised of activating the fibrinolytic system only at the site of thrombus formation and thereby not inducing systemic fibrinolysis? Also, is it reasonable to investigate whether it is a good strategy to design or identify an agent that acts only at the site of thrombus formation? Moreover, having studied the activity of newer agents in vivo, is it reasonable to expect a reduction or an elimination of the undesirable problem of bleeding? Are these second-generation thrombolytic agents thrombus-specific, target-specific, or fibrin-specific?

None of the second-generation thrombolytic agents are capable of selectively specifically activating the fibrinolytic system at the site of thrombus formation, and they all induce systemic activation of the entire fibrinolytic system.

As shown in Figure 1, when plasma fibrinogen is quantified during the infusion of each of the second-generation thrombolytic agents (the agents are given in the standard dose for treatment of myocardial infarction and infused over a 3-hour interval for rt-PA, 60 minutes for streptokinase and urokinase, and 5–10 minutes for APSAC), a progressive reduction in the plasma fibrinogen concentration is easily observed. The decline is greatest for APSAC and streptokinase, whereas the degree of decline is very similar for urokinase, rt-PA, and r-proUK. rt-PA, in addition to generating plasmin, can directly degrade purified fibrinogen in the absence of plasminogen.[70] If the thrombolytic agents rt-PA, APSAC, or r-pro-UK were "fibrin-specific" in their actions, there would be no interaction with circulating fibrinogen; this, however, is not what was found following the institution of these thrombolytic agents in humans.

As is clearly evident in Figure 2, plasma-plasminogen also undergoes a progressive reduction in concentration following the institution of APSAC, rt-PA and r-pro-UK. The reduction is most pronounced for APSAC and streptokinase. If the agents rt-PA, r-pro-UK, and APSAC were fibrin-specific they would activate the plasminogen associated with fibrin. However, as shown in Figure 2, plasma-plasminogen freely circulating in the blood is significantly reduced below the normal concentration. If these agents interacted only with fibrin-associated plasminogen there would be no reduction in circulating plasma-plasminogen.

As shown in Figure 3, all available thrombolytic agents, including APSAC, rt-PA, and r-pro-UK, generate enormous quantities of FDP-fdp. These data establish without question that none of the second-generation thrombolytic agents are capable of selectively specifically activating the fibrinolytic system at the site of thrombus formation and that they all induce systemic activation of the entire fibrinolytic system.

In addition, we observed, following the institution of rt-PA, a progressive increase in the plasma level of the adhesive von Willebrand protein, as determined by the immunologic Laurell rocket technique.[71] The increase was linear during the 3-hour infusion of the rt-PA compound. Increases were not observed in association with the infusion of streptokinase, urokinase, APSAC, or r-pro-UK.

In the Thrombolysis in Myocardial Infarction (TIMI) Phase I study,[72,73] it was observed that approximately 10% of patients receiving rt-PA became thrombocytopenic in contrast to < 1% of patients receiving streptokinase. This problem associated with rt-PA has been observed by other investigators.[74]

In an attempt to identify how the rt-PA compound was interacting with platelets, we observed, using in vitro studies, that rt-PA inhibited the platelet aggregation of ristocetin. The degree of inhibition was progressively more severe as the concentration of rt-PA was increased.[75] We also observed that the synthesis of thromboxane-A2 was inhibited and C14-serotonin release were not observed in the presence of a variety of concentrations of urokinase and streptokinase. Bennett and colleagues[76] have observed in association with infusions of rt-PA but not invasive manipulatory procedure of cardiac catheterization a prominent increase in the activation of the C3a, C4a, and C5a components of the complement system. We have not seen these changes in association with urokinase or streptokinase.

It is apparent from these studies that the rt-PA agent is not appreciably fibrin- or thrombus-specific and in addition, in a rather promiscuous manner, it activates the complement system and binds to and damages the membranes of platelets and vascular endothelial cells.[77,78]

Activating the Fibrinolytic System

Although currently available thrombolytic agents do not possess fibrin-,

thrombus- or target-specificity, the question must be asked whether it is a good strategy to try to design an agent that will not give rise to the systemic activation of the fibrinolytic system. When studies of whole blood and plasma viscosity were performed before and during infusions of streptokinase and urokinase, as well as in patients receiving rt-PA, it was observed that in association with streptokinase whole-blood viscosity at shear rates of 50/sec and 0.5/sec was reduced from 5.1 centipoise to 3.8 centipoise and from 3.8 centipoise to 1.9 centipoise, respectively. In addition, plasma viscosity in association with streptokinase was reduced significantly from 1.4 centipoise to 0.86 centipoise. These observations were also identified with urokinase. No significant reductions in identical studies could be observed in patients receiving rt-PA.

Although the observation has not been clearly established, it may be that a reduction in blood and plasma viscosity at the time of left-ventricular insult, myocardial infarction, or severe ischemia may be beneficial. At this time of myocardial damage the ejection force and blood flow are critically important. If, however, there is a simultaneous reduction in viscosity at the time of left-ventricular insult with a lower ejection force, it is possible that a normal or near-normal blood flow may be maintained. This is clearly important in order to facilitate a more rapid recovery via nutrition and oxygenation to the myocardium, with a normal and near-normal rate of blood flow reduced below normal. Such a thrombogenic environment associated with a reduced blood flow may more frequently predispose a patient to reocclusion of the coronary vessels following patency induced by thrombolytic therapy.

Bleeding associated with thrombolytic therapy, regardless of the thrombolytic agent employed, is most frequent at invaded sites (eg, sites used for cardiac catheterization, arterial blood-gas studies, intracath insertion or IV infusion, or venepuncture for blood studies of any type). At any invaded site, the vascular endothelium is disrupted; therefore, an inflammatory reaction takes place. The major components of an inflammatory reaction are fibrin and two different cell types that form the hemostatic plug. It has been established that the fibrin in the hemostatic plug is identical to the fibrin in a pathologic thrombus in very freshly (recently) formed thrombi and much more susceptible to dissolution. Thus, if a "fibrin-specific" thrombolytic agent is infused into the circulation it will interact with molecularly identical fibrin in both the hemostatic plug and the pathologic thrombus, and this may promptly bring about the dissolution of the hemostatic plug, thereby inducing bleeding. This may be the reason why in all recently completed studies comparing first- and second-generation thrombolytic agents, there is as much bleeding with the newer, second-generation agents as with the older ones. In fact, there may be more bleeding with the newer agents than with the first-generation agents streptokinase and urokinase.

It is apparent from these studies that the rt-PA agent is not appreciably fibrin- or thrombus-specific and in addition, in a rather promiscuous manner, it activates the complement system and binds to and damages the membranes of platelets and vascular endothelial cells.

Thrombolytic Agents in the Treatment of Myocardial Infarction

A comparison of the clinical efficacy of the newer thrombolytic agents with the first-generation thrombolytic agents can best be made by evaluating studies performed in the treatment of myocardial infarction, where all currently available thrombolytic agents have been employed. A large number of well-designed prospective, randomized, blinded, and appropriately controlled studies have been conducted employing thrombolytic therapy in the treatment of myocardial infarction.

The opening of the coronary artery or infarct-related coronary arteries occurs with all agents in the range of approximately 50%–85% of patients, and one agent does not differ from the others with one exception, ie, in the TIMI Phase I study[77,78] rt-PA demonstrated greater patency than streptokinase did. With respect to hemorrhage, bleeding occurs unquestionably as frequently with the newer agents as with the older ones, and as more studies are being completed, the newer agents may be found to be associated with more bleeding than urokinase and streptokinase. This was particularly evident in the recently completed International Study of Infarct Survival (ISIS-3) study, which demonstrated greater patency with rt-PA than with streptokinase. With respect to hemorrhage, more was seen in patients receiving rt-PA and APSAC than those who received streptokinase. Studies have shown that the frequency of reocclusion appears to be greatest in those patients who receive the rt-PA compound.

All very large population studies

(10,000 or more patients) have demonstrated a reduction in mortality associated with thrombolytic therapy in contrast to placebo, control therapy. This reduction has been observed with all thrombolytic agents, and no thrombolytic agent has a greater reduced mortality than any other thrombolytic agent. The one exception mentioned above, ie, the TIMI Phase I study,[72,73] is the only one of these studies that was not carried out to completion as it was stopped before the predesigned patient-accession number was achieved. It is also the only one of all the comparative studies whose results have not been able to be reproduced in any other study.

Physicians currently knowledgeable about these results are aware that thrombolytic therapy can induce dissolution and complete resolution of thrombi and emboli. With knowledge of the properties of the various thrombolytic agents available today, the physician can intelligently select the optimal agent for a given patient problem. ■

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Main Points

- Human tissue plasminogen activators (rt-PA) are endogenously synthesized and secreted by vascular endothelial cells as a glycosylated protein. The recombinant molecule (rt-PA) that is employed therapeutically becomes activated when Arg_{275}-Ile_{276} is cleaved. Once activated, it can activate its substrate plasminogen at the identical site acted upon by streptokinase and urokinase.
- The degradation products of fibrinogen or fibrin (FDP-fdp) are the absolute index to the activity of the fibrinolytic system in man. When the degradation products of FDP-fdp reach excessive quantities in the circulating blood, they are easily detected and unequivocally establish intense activation on a systemic level of the plasminogen-plasmin proteolytic enzyme system.
- Marked changes in levels of concentration of fibrinogen, plasminogen, and FDP-fdp observed in the circulating blood following the administration of streptokinase and urokinase unequivocally establish the presence of systemic activation of the fibrinolytic system.
- None of the second-generation thrombolytic agents are capable of specifically activating the fibrinolytic system at the site of thrombus formation, and they all induce systemic activation of the fibrinolytic system.
- Bleeding occurs as frequently with the second-generation agents as with the older agents. Further studies may even show that bleeding occurs more frequently with the newer agents than with urokinase and streptokinase.
- It is apparent from these studies that the rt-PA agent is not appreciably fibrin- or thrombus-specific and in addition, in a rather promiscuous manner, it activates the complement system and binds to and damages the membranes of platelets and vascular endothelial cells.

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