Review of Pharmacology and Physiology in Thrombolysis Interventions

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ABSTRACT

Reperfusion therapy using thrombolytic agents has been shown to be a safe and effective treatment strategy for arterial ischemia, venous thrombosis, massive pulmonary embolism, and acute stroke. Thrombolytic agents have evolved over the course of a few decades, from nonfibrin selective to fibrin-selective agents. The development and modification of these agents have resulted in improved understanding of their pharmacologic attributes, and their effects on the complex molecular events that occur during thrombolysis goal-directed therapies. The current review focuses on the physiology and pharmacology of the thrombolytic agents that have been or are currently in use for interventional thrombolysis interventions. Attention is also given to the particular role that thrombolytic agents play in the current management of peripheral vascular disease and acute stroke.

KEYWORDS: Catheter-directed thrombolysis, pharmacology, physiology, acute limb ischemia, stroke

Objectives: Upon completion of this article, the reader will be able to identify the physiology and pharmacologic differences that exist between the agents used in catheter-directed thrombolysis, with particular attention to their use in the management of acute limb ischemia and stroke.

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PHYSIOLOGY OF HEMOSTASIS AND FIBRINOLYSIS

Physiologic hemostasis involves a delicate balance of three processes: coagulation or clot formation, fibrinolysis or dissolution of clots, and naturally occurring serine protease inhibitors that regulate the enzymatic activity of both the coagulative and fibrinolytic processes. This complex system is driven by two major components:

plasma proteins and the cellular constituent of platelets, endothelial cells, neutrophils, and monocytes.

Hemostasis

Vessel wall injury exposes subendothelial collagen and tissue factors to initiate the extrinsic pathway of the coagulation cascade. Platelets then adhere to the site of

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injury with the aid of the von Willebrand factor and a signaling cascade is initiated within these cells, leading to the release of granule contents. These molecules stimulate the coagulation cascade bringing thrombin to the platelet surface. Thrombin formation and platelet activation leads to platelet aggregation and formation of a hemostatic plug. Activation of the intrinsic pathway occurs when contact is made between negatively charged blood surfaces; this also leads to stimulation of the coagulative cascade and plug formation (Fig. 1).

Fibrinolysis

The fibrinolytic system consists of a network of proteins that provide regulation to the hemostatic mechanism by maintaining the patency of the vessel wall through opposition of the coagulation cascade. This regulatory system includes plasminogen, a zymogen or inactive enzyme precursor, and naturally occurring plasminogen activators, such as tissue plasminogen activator (tPA). Plasmin circulates as the inactive precursor form of plasminogen. The binding of fibrinogen converts plasminogen into a configuration that promotes its further activation by surrounding plasminogen activators and increases the efficiency of fibrinolysis. The plasminogen activators cleave a specific component of the plasminogen molecules to generate the active compound, plasmin. Cleavage of fibrin by plasmin then generates a substrate of fragments that all function to activate the antithrombotic properties of plasmin.

HISTORY OF THROMBOLYTIC THERAPY

First-Generation Thrombolytic Agents

In 1933, Tillett and Garner first discovered that filtrates isolated from certain strains of hemolytic bacteria could dissolve fibrin clot.¹ In the late 1940s, Tillett and Sherry dissolved loculated hemothoraces by administering streptokinase intrapleurally.² In 1955, Tillett et al intravenously injected a partially purified and concentrated streptokinase, which led to systemic proteolysis, decreased fibrinogen and plasminogen, and increased prothrombin time.³ However, because streptokinase is a bacterial protein, this was not without antigenic-related systemic effects of fever and hypotension. In 1974, Dotter et al published an article utilizing a low-dose protocol for the administration of streptokinase in an effort to decrease the overall antigenicity and enhanced lytic state created by streptokinase. However, frequent bleeding due to an intense systemic proteolytic state still occurred and prompted investigation for an alternate treatment.⁴

Streptokinase activates plasmin via a fibrin-dependent and fibrin-independent mechanism, therefore degrading fibrinogen along with other proteins that all serve to enhance the “lytic” state. The adverse effects and

nonfibrin selectivity have curtailed its use in the United States.

In 1947, Macfarlane and Pilling first described the fibrinolytic potential inherent in human urine.⁵ In 1952, Sobel et al were able to extract and isolate the active molecule, coining the term “urokinase.”⁶ This compound activated the fibrinolytic system without evoking an antigenic response, consequently making fever and hypotension rare occurrences. In contrast to streptokinase, urokinase activates plasminogen directly. However, urokinase lacks fibrin selectivity again resulting in a severe “lytic” state.⁶

Second-Generation Thrombolytic Agents

Tissue plasminogen activator is a natural fibrinolytic agent produced by endothelial cells that is involved in maintaining the delicate intravascular balance of thrombolysis and thrombogenesis. Structurally, naturally occurring tPA is a 527-amino acid single-chain serine protease with considerable activity (Fig. 2).

It has fibrin specificity, as it does not activate plasminogen freely floating in blood. On a molecular level, the binding of both tPA and plasminogen to the fibrin surface of a blood clot induce a conformational change in the two molecules. This change subsequently accelerates the conversion of plasminogen to plasmin and subsequent dissolution of thrombus. In addition to fibrin specificity, tPA exhibits strong binding to fibrin, also known as fibrin affinity. Therefore, in addition to using fibrin, the plasmin at the clot surface also enhances the conformational change that further accentuates the enzymatic activity of tPA. The commercially available form of tPA is produced using recombinant technology and is called alteplase (r-tPA); rtPA has been approved by the Food and Drug Administration (FDA) for acute myocardial infarction, acute stroke, massive pulmonary embolism, and central venous catheter occlusion. It has also been widely used (although off-label) for catheter-directed venous and arterial thrombolysis.

Third-Generation Thrombolytic Agents

To improve upon tPA, modification of three amino acid enzymatic sites produced tenecteplase, or TNK-tPA, to increase fibrin specificity and prolong its half-life (Fig. 2). Increasing fibrin specificity leads to less depletion of fibrinogen, whereas prolonging the half-life allows for single bolus administration rather than continuous intravenous (IV) infusion.⁸ To further simplify administration of a thrombolytic, the development of reteplase or reteplase targeted decreasing affinity to hepatocytes and reducing fibrin-binding activity. Decreased affinity to hepatocytes was hypothesized to prolong drug half-life, thus enabling single bolus administration. Several deletions of domains of the tPA molecule resulted in the

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death. The two most common etiologies behind non-traumatic ALI are arterial thrombosis, in the context of atherosclerotic vascular disease, and arterial embolus, usually of cardiac origin. Arterial thrombosis predominantly affects the lower extremities because the upper extremities have an extensive and rich collateral blood supply. Patient outcome and prognosis are largely dependent upon the rapid diagnosis and delivery of appropriate treatment in a safe and timely fashion.

Over the past several decades, preferred treatment options for patients with ALI have alternated between

Figure 2 Molecular structure of the second-generation compound, alteplase, which is the predominant thrombolytic agent used across the United States. The arrows point to the amino acid modification sites in the creation of tenecteplase, the third-generation compound. (Picture courtesy of Genentech.)

surgical intervention and medical approaches. Intraarterial catheter-directed thrombolysis can achieve thrombus dissolution, with subsequent recanalization of the occluded vessel and unveiling of an underlying lesion that can then be treated endovascularly. However, one must take into consideration that the clinical success of thrombolysis management can lead to delays in achieving arterial reperfusion.

Two landmark prospective, randomized, multicenter clinical trials deserve mention in the approach to patients with ALI. In the STILE (Surgery versus Thrombolysis for Ischemia of the Lower Extremity) Trial, patients with nonembolic native artery or bypass

graft occlusion in the lower limbs who presented with clinical symptoms of 14 days or less experienced lower rates of amputation and death following catheter-directed intraarterial thrombolysis with tPA or urokinase as compared with surgical intervention.⁹ Furthermore, at 6-month follow-up, there was an improved amputation-free survival in the thrombolysis group. The TOPAS (Thrombolysis or Peripheral Arterial Surgery) Trial also identified intraarterial catheter-directed thrombolysis using urokinase to be a safe and effective treatment compared with surgery in acute arterial occlusion, also with comparable rates of amputation-free survival and death.^{10,11} However, the TOPAS Trial did show a higher frequency of hemorrhagic complications in urokinase-treated patients, which is probably attributed to its lack of fibrin selectivity as described earlier. Despite this increased rate of hemorrhagic complications in the thrombolysis group, the need for open surgery was diminished with no significant risk of amputation or death.

Lansdale et al performed a nonrandomized comparative trial examining the effects of intraarterial streptokinase and tPA with arterial occlusion.¹² Rates of amputation and death were lower in tPA-treated patients (41% vs 59%), along with a shorter time to lysis (22 hours vs 40 hours). Since the STILE and TOPAS trials, a consensus proposal by a Working Group including angiologists, hematologists, interventional radiologists, and vascular surgeons from North America and Europe proposed that thrombolytic treatment should be considered as an acceptable treatment option in patients with acute arterial occlusion in native vessel or in bypass grafts.¹³ These recommendations are as follows:

1. In patients with native artery occlusion, thrombolysis followed by correction of the underlying causative lesion is an appropriate strategy in patients presenting with ischemic symptoms <14 days.
2. Surgical revascularization should be performed immediately if thrombolysis would delay effective limb reperfusion.
3. Patients with irreversible ischemia should undergo primary amputation.

Table 1 Table Illustration of Characteristics of First-Generation, Second-Generation, and Third-Generation Thrombolytic Agents

	First-Generation (Streptokinase)	Second-Generation TPA (Alteplase)	Third-Generation (Reteplase)
Molecular weight (Daltons)	47,000	70,000	39,000
Half-life (min)	23	<5	13–16
Bolus administration	No	No	Yes
Allergic response	Yes	No	No
Fibrin selective	No	Yes	Yes
Plasminogen binding	Indirect	Direct	Direct

4. For occluded bypass grafts, options are surgical revision and thrombectomy, catheter-directed thrombolysis, or insertion of a new graft.

Vascular Graft Occlusions

A subgroup analysis of the STILE Trial data did show that thrombolysis appears to be more effective when used in the treatment of graft occlusions than when used for native artery occlusions.^{9,14} As with native arterial occlusions, the Working Group recommendations also involve additional factors that relate to the nature of the graft, duration and degree of ischemia.

Clear differences in the superior patency rates of vein grafts over polytetrafluoroethylene (PTFE) grafts have been reported in the literature. Primary patency rates at 4 years for infrapopliteal bypasses with saphenous vein have been measured at 49%, a significantly higher rate than the 12% patency rates associated with PTFE grafts.¹⁵ When considering thrombolytic interventions, it is important to understand the difference in the nature of thrombotic occlusions in both vein and prosthetic bypass grafts. Thrombotic occlusions can occur with both types of bypass grafts due to underlying technical problems, such as stenoses at insertion sites, which can progressively delay antegrade blood flow through the system. Both types of grafts are also affected by underlying progressive atherosclerotic disease that can alter the hemodynamics of inflow and outflow through the graft entry and exit points. Neointimal hyperplasia also plays a role in vascular occlusion, but differs in extent. For example, neointimal hyperplasia of vein grafts can lead to either a diffuse luminal reduction in graft caliber, or can lead to a focal isolated stenosis from either surgical anastomotic sites or at venous valves sites.^{16,17} In contrast, the intimal hyperplasia that develops in PTFE grafts tends to occur predominantly at the anastomotic sites from the adjacent artery. Vein bypass occlusions tend to occur less frequently than PTFE grafts because they are lined with endothelium that allows maintenance of the antithrombotic regulatory mechanism.^{16,17} PTFE grafts, however, are highly thrombogenic at the time of implantation and remain so as long as they are in place (Fig. 3). Further studies looking at different materials for graft prosthetics are still being developed.

Dosage and Delivery

IV administration of thrombolytics should not be performed for ALI, as there is a high incidence of hemorrhagic complications concurrent with poor outcomes. Patients who undergo intraarterial catheter-directed therapy usually undergo the guidewire test,

initially proposed by McNamara and Fischer.⁷ This test detects the ease with which a guidewire can be passed into an area of occluded native artery or bypass graft. A wire that passes easily through the occlusion indicates the presence of an acute thrombus with a high probability of successful lysis. Once the guidewire crosses across the occluded segment, a thrombolysis infusion catheter can be advanced into the occluded segment and appropriate thrombolysis treatment initiated.

A multicenter randomized trial by Braithwaite et al compared high-dose bolus administration of tPA (3–5 mg bolus doses, then 3.5 mg/h for a maximum of 4 hours, followed by 0.5–1.0 mg/h) versus low dose tPA (0.5–1.0 mg/h) in patients with acute leg ischemia.¹⁸ No statistically significant differences were seen between the two groups in terms of limb salvage or complication rates. The Advisory Panel on Catheter-Directed Thrombolytic Therapy in 1999¹⁹ has since provided guidelines for the use of tPA. Suggested dosing regimes are either a weight-adjusted dose of 0.001–0.2 mg/kg/h or a nonweight-adjusted dose of 0.12–2.0 mg/h. Maximum total dose should be no greater than 40 mg for catheter-directed therapy.²⁰ The authors' preference is a low-dose regimen of 0.5 mg–1.0 mg/h.

Complications

One of the most significant complications encountered during catheter-directed arterial thrombolysis is bleeding, particularly intracranial hemorrhage. Bleeding complications lead to significant morbidity, such as lengthy hospital stays and multiple transfusions. The International Study Group (1990) and the Collaborative Group (1988) have reported that bleeding rates associated with treatment of acute myocardial infarction are less than 5%; however, bleeding rates associated with catheter-directed techniques are usually greater than 5%.^{21,22} This occurs despite the fact that the total lytic dose administered for treatment of acute myocardial infarction is higher than that for catheter-directed lysis.

One important concept introduced by Swischuk and Smouse to explain this discrepancy is that a distinction should be made of two separate processes: fibrinolysis—the breakdown of crosslinked fibrin and fibrinogenolysis—the breakdown of freely circulating fibrinogen.²³ tPA, like other lytic agents, causes fibrinolysis that involves the breakdown of fibrin into fibrin degradation products (FSPs). One moiety of FSPs subsequently enters the circulation and functionally serves to stimulate tPA activation of systemic plasminogen to plasmin, which in turn breaks down further fibrin. This extra moiety also breaks down freely circulating fibrinogen, leading to fibrinogenolysis.

Figure 3 A 65-year-old woman presented with acute limb ischemia of 5-days duration. She was referred for thrombolytic intervention. (A) Digital subtraction angiography (DSA) of the proximal left lower extremity demonstrates patent superficial femoral and profunda femoral arteries. (B) DSA centered over the knee demonstrates site of proximal surgical anastomosis (arrow) of popliteal-anterior tibial bypass vein graft. There is little antegrade flow through the graft. There is abrupt occlusion of

During fibrinogenolysis, various degradation products are created. One of the fragments produced has been shown in multiple experimental and clinical studies to play a role in the occurrence of bleeding during catheter-directed thrombolysis. This entity decreases the strength of thrombus hemostatic plug in a concentration-dependent fashion, such that higher levels of this product lead to acceleration of clot lysis.²⁴ It is believed that this fragment may be incorporated in any existed thrombus including a distant hemostatic plug, thus leading to increased rates of distant bleeding. Clinically measuring fibrinogen levels, therefore, does not reliably predict bleeding complications because it is only a small factor in the cascade of events occurring at a molecular level contributing to possible bleeding. Measuring specific FSPs is not realistic in the typical hospital setting.

Precautions need to be taken even when using the more specific fibrin-specific drugs. Swischuk and Smouse (2005) demonstrated that using tPA in doses greater than 1.5 mg/h in conjunction with full heparinization led to higher rates of major bleeding.^{23,25} Their subsequent report in a nonrandomized dose ranging study demonstrated that using lower doses of tPA as outlined earlier with subtherapeutic heparinization significantly reduced bleeding. Therefore, the newer fibrin-specific agents such as tPA should be used with caution because they have a relatively narrower window of dosing safety. The authors' preference is to use tPA with subtherapeutic heparinization at rates of 200 to 400 units per hour.

tPA AND ITS ROLE IN THE TREATMENT OF STROKE

A majority of ischemic strokes are either thrombotic and/or thromboembolic in nature. The clinical application of thrombolysis has been a long-studied phenomenon with major breakthroughs occurring only within the last two decades. The first study to claim that tPA is effective in the treatment of acute ischemic stroke was a multicenter clinical trial coordinated by the National Institute of Neurological Disorders and

Stroke (NINDS) Study Group.²⁶ An effective thrombolytic therapy necessitates the recognition of a therapeutic window; this window is challengingly brief in ischemic stroke as neuronal death and brain infarction evolve progressively in a time-dependent fashion, determined by both duration and severity of the ischemic insult.²⁷⁻²⁹

Since the landmark report from the National Institute of Neurological Disorders and Stroke (NINDS) demonstrated substantial benefit from the careful use of IV tPA in patients with ischemic stroke, the use of IV tPA within the first 3 hours of onset of acute ischemic stroke has received regulatory approval in the United States, Canada, Europe, Australia, and many Asian countries. A meta-analysis has concluded that IV thrombolytic therapy within 3 hours of symptoms onset significantly reduced the number of patients suffering the endpoint of death or dependency.³⁰ Meta-analysis restricted current IV protocols, such as the Cochrane stroke group, also demonstrated a much more favorable trend toward the use of tPA within the first 3 hours.³⁰

Other studies that have analyzed tPA trials that were initiated >3 hours after onset of symptoms have concluded that there was substantial evidence of benefit for tPA therapy delivered within the first 180 minute, with evidence of declining benefit up to 4.5 hours. Once the time interval is in excess of >4.5 hours, the benefit of IV tPA therapy becomes small.³⁰ Therefore, the implications of early treatment are profound and require the clinician to provide rapid evaluation, imaging and treatment, all preferably within 3 hours, with a diminishing small benefit persisting for up to 4.5 hours. Effective thrombolytic therapy is accompanied by a set of approved inclusion/exclusion criteria (Table 2).³⁰

Thrombolytics are frequently delivered by an IV route; however, other modes of delivery have shown promising results. In severe cases like basilar artery occlusion, where mortality rates are as high as 80 to 90%, more aggressive therapy may be warranted.³¹⁻³⁵ Intraarterial catheter-directed thrombolysis therapy may be delivered directly into the thrombus using

Figure 3 (Continued) the native popliteal artery above the level of the trifurcation with multiple small collateral vessels seen coursing around the midcalf. (C) DSA centered over the distal calf demonstrates a distal surgical anastomosis (arrow), with poor flow seen coursing through the graft. Multiple collateral vessels are again visualized around the midcalf region. (D) Roadmap magnified view of the proximal anastomosis demonstrates positive "guidewire test" in which a guidewire was able to be successfully introduced through the proximal end of the graft, indicating acute thrombus. A thrombolysis infusion catheter was placed for infused therapy at this proximal level (arrow). (E) Follow-up DSA after 2 days of thrombolysis demonstrates good antegrade flow through the vein bypass graft, with visualization of underlying defect (i.e., tight stenosis) at the proximal graft anastomosis. (F) Follow-up angiogram after 2 days of thrombolysis demonstrates visualization of flow through the distal end of the graft through the anterior tibial anastomosis, and into the foot as the dorsalis pedis artery. (G) Magnified view of the proximal anastomosis reveals adequate and successful placement of stent across the stenotic segment of the proximal anastomosis. Excellent flow is seen through the bypass graft. (H) Follow-up DSA after 3 days of thrombolysis demonstrates good antegrade flow through the entire length of the popliteal-anterior tibial artery bypass graft.

Table 2 Eligibility Criteria for Consideration of Intravenous tPA Thrombolysis (Grade IA) in the Setting of Acute Stroke

Inclusion Criteria	Exclusion Criteria
Age >18 years	Minor or rapidly improving signs or symptoms
Clinical dx of stroke with clinical neurologic deficit	CT signs of intracranial hemorrhage
Clearly defined time of onset of <180 min before treatment	Seizure at stroke onset
Baseline CT showing no hemorrhage	Stroke or serious head injury in the past 3 months
	Major surgery or serious trauma in past 3 months
	GI or urinary tract hemorrhage within 3 weeks
	Systolic BP >185 or diastolic >110 or aggressive tx required to lower BP
	Glucose <50 or >400
	Symptoms of subarachnoid hemorrhage
	Platelets <100,000; INR >1.7: elevated PTT
	Clinical presentation suggesting postmyocardial pericarditis
	Pregnancy
	Lumbar puncture within 1 week

BP, blood pressure; CT, computed tomography; dx, diagnosis; GI, gastrointestinal; INR, international normalized ratio; PTT, partial thromboplastin time; tx, treatment

selective catheters. Intraarterial therapy allows for a local thrombolytic drug delivery directly onto the clot and access for mechanical clot disruption. This offers the added potential advantages of increased recanalization rates, improved accuracy of diagnosis, and reduction in the amount of drug administered thus increasing the safety profile of the thrombolytic agent.³⁰ The use of intraarterial thrombolytic therapy is currently limited to facilities with personnel who are capable of performing this procedure with precision, and which offer adequate preprocedural and postprocedural care to patients. There is limited evidence to provide recommendations for proper intraarterial thrombolytic agent, dose, delivery technique, or duration of therapeutic window; these limitations are bound to change in the near future as more trials are currently under scrutiny. A highly variable therapeutic window has been demonstrated and this will be significantly altered with intraarterial thrombolysis. Some cases of basilar artery occlusion have shown exceptional recovery even for up to 12 hours after onset of symptoms.³⁰ Current guidelines note that IA thrombolysis is reasonable in patients who have contraindications to IV thrombolysis.³⁰

New and investigational therapies using tPA in the context of ischemic stroke include novel ideas like combination therapy with abciximab, a monoclonal antibody with platelet glycoprotein IIb-IIIa receptor, or a combination IV/IA tPA therapy. Mechanical devices are also used as an adjunct to expedite clot lysis or extraction. The concentric MERCI retriever system has received FDA-approval for clot retrieval in acute ischemic stroke based on the result on the MERCI trial, which showed up to 46% recanalization rates,

compared with a historical control rate of 18%.³⁶ Another innovative approach uses transcranial Doppler sonography to enhance the thrombolytic effect of tPA. Data for most of these innovative ideas are insufficient and further clinical trials are needed before they can be recommended for the treatment of acute ischemic stroke.

CONCLUSION

The native thrombolytic system, involving a balanced interaction between hemostasis and fibrinolysis, can be enhanced via the administration of pharmacologic agents that aid in intensifying the breakdown of thrombus/embolus by the production of a "lytic" state. This "lytic" state occurs predominantly via the ultimate activation of plasminogen. Ever since streptokinase became available, modifications have been made biochemically in efforts to improve the specificity and efficiency of thrombolytic agents, and to minimize overall complication rates. Although all thrombolytic agents ultimately result in the dissolution or fragmentation of thrombus, these agents differ in their pharmacologic properties. The management of patients with thromboembolic disease can be complex, and it is important to understand the physiologic mechanisms that are undertaken when using thrombolytics in various interventional treatment strategies.

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