Thrombolytic Agents

David Green

Northwestern University Medical School, Chicago, Illinois, U.S.A.

*T*hrombus dissolution is dependent on activators of plasminogen, the principal enzyme of fibrinolysis, reaching plasminogen bound to the surface of fibrin, and overcoming the many inhibitors of clot lysis present in the plasma milieu. In dialysis patients with occluded catheters and grafts, three activators — streptokinase, urokinase, and tissue plasminogen activator (tPA) — have been used. Streptokinase has fallen out of favor because of its adverse effect profile; urokinase has been the mainstay of therapy. Urokinase has been used alone and in conjunction with mechanical methods for clearance of thrombi from arteriovenous grafts. It has also been instilled into occluded central venous catheters, but often is more effective if given systemically during dialysis in order to lyse the fibrin sheath that surrounds the catheter tip. Due of manufacturing problems, urokinase is no longer available and management with tPA is being actively investigated. One small trial showed that recombinant tPA was significantly more effective than urokinase for restoring catheter patency, but the drug is not yet approved for this purpose by the FDA, and current packaging is not optimal. The problems with thrombolytic agents may be obviated in the future by better methods of prevention of thrombus formation, monitoring flow to anticipate occlusion, and early mechanical interventions to restore patency.*

Key words

Introduction

Thrombus dissolution is a complex physiological event based on activation of plasminogen, the principal zymogen of the fibrinolytic system. Natural activators of plasminogen are urokinase and tissue plasminogen activator (tPA); bacterial activators include streptokinase and staphylokinase.

Correspondence to:

David Green, MD, PhD, Northwestern University Medical School, 345 East Superior Street, Room 1407, Chicago, Illinois 60611 U.S.A.
email: d-green@nwu.edu

Streptokinase

Streptokinase was isolated in 1933 and has been used as a thrombolytic agent since 1959 [1]. It forms a complex with plasminogen, and this streptokinase–plasminogen complex catalyzes the conversion of plasminogen to plasmin, the active fibrinolytic enzyme. Doses are 10 000 – 100 000 IU/hour and result in complete clot lysis in 50% – 70% of patients. Failure of lysis may be due to the drug not being able to access plasminogen on the fibrin clot, or to pre-existent antibodies to streptococcal proteins. Adverse reactions include fever, bleeding, rash, hypotension, bronchospasm, and, occasionally, serum sickness syndrome.

Anisoylated plasminogen streptokinase activator (APSAC)

Because the streptokinase–plasminogen complex is rapidly inactivated in plasma, APSAC was created. Anisoylation protects the active site of the complex from inactivation, enhancing the half-life of activity. *In vivo*, the compound is rapidly deacylated, generating the active complex. While there have been several trials of this agent in the treatment of acute myocardial infarction, studies of venous thrombosis have not been reported. The adverse effect profile is similar to that of streptokinase.

Urokinase

Urokinase is derived from urine and kidney cells. It is a serine protease composed of two chains joined by a disulfide bridge. The precursor molecule, single-chain urokinase (scuPA) is also active. Urokinase is inhibited by plasminogen activator inhibitors, and protease nexin-1. A receptor for urokinase on endothelial cells (uPAR) may modulate urokinase activity by removal of urokinase-plasminogen activator-inhibitor complexes. Both two-chain and single-chain urokinase are more active in the presence of fibrin and heparin. Urokinase has been used for clearance of thrombi from arteriovenous grafts. Catheters may be advanced into the thrombus and the thrombus pulse-sprayed with a heparin–urokinase mixture; this ensures that the lytic agent is maximally active and in contact with fibrin throughout the thrombus [2]. The National Kidney Foundation–Dialysis Outcomes Quality Initiative (Guideline 21) suggests that this technique should result in immediate patency — defined as patency to the next dialysis session — of 85%, and 40% unassisted patency and

functionality at 3 months. It is also emphasized that thrombosis is associated with underlying venous stenosis in most instances, and it is imperative to attempt to relieve the stenosis.

Several studies have demonstrated the efficacy of urokinase in restoring the patency of dialysis catheters [3,4]. In 1998, Seddon *et al*. filled catheter lumens with urokinase for dwell times of up to an hour, and then repeated the dose of urokinase to ensure the clot was fully exposed to the agent [4]. The formation of an extensive fibrin sheath surrounding the catheter tip often thwarts this method, and argues for the use of systemic thrombolytic therapy. Recently, Twardowski [5] reported that a 3-hour infusion of 250 000 IU of urokinase during dialysis was effective in restoring pump speed in 132 of 162 instances. Repeating the urokinase infusion during the next dialysis in cases where the first infusion was not completely effective usually restored flow.

Systemic treatment with urokinase should not be given to patients who have had major surgery within the previous 2 weeks, or a stroke within the previous 3 months. It is also contraindicated in those with active ulcers or other potential bleeding lesions, recent severe trauma, or recent organ biopsies. Other contraindications are uncontrolled hypertension, hemorrhagic retinopathy, bacterial endocarditis, and pregnancy. Patients with thrombi in the heart or elsewhere may have embolization of those clots, and infected thrombi in dialysis catheters or fistulas may embolize to internal organs. Patients should be closely monitored during infusions for signs of bleeding and observed for evidence of allergic reactions (fever, bronchospasm, skin rash).

Tissue plasminogen activator

Tissue plasminogen activator is a single-chain serine protease with a molecular weight of 68 kD. It binds to fibrin and then activates plasminogen to plasmin; tPA activity is increased two- to threefold in the presence of heparin. The binding of tPA to fibrin and its activation of plasminogen are inhibited by plasminogen activator inhibitor (PAI-1).

The efficacy and safety of tPA in restoring patency of occluded central venous access devices was evaluated in 6 subjects after failure of 10 000 IU of urokinase [6]. Recombinant (r)tPA in up to two 2-mg doses was successful in restoring function in 5 of the 6 patients. No evidence of fibrinogen breakdown or bleeding was observed. In a subsequent larger investigation, 50 subjects with radiographically proven thrombosed catheters received either two doses of 2 mg tPA or 10 000 IU urokinase instilled into the catheters, with a dwell time of 2 hours following each dose [7]. Up to two doses of urokinase were successful in restoring function in 59% of dysfunctional catheters. Recombinant tPA was significantly more effective, providing restoration of flow

in 89% ($p = 0.013$). Radiological study showed that 7 catheters randomized to urokinase had complete resolution of the thrombus, compared to 17 randomized to rtPA ($p = 0.036$). No adverse effects were reported and no decreases in fibrinogen levels were noted.

These excellent results with rtPA, from a single institution, need to be replicated in a multicenter trial. Furthermore, tPA is currently marketed in a 50-mg vial, so that the use of 2 mg or 4 mg is likely not cost-effective. However, if an access catheter is found to be occluded by thrombus, and changing the catheter over a guide wire is not feasible, rtPA would be a therapeutic option.

Investigational thrombolytic agents

Staphylokinase

Staphylokinase forms a 1:1 stoichiometric complex with plasminogen, which results in plasmin formation. The activity of staphylokinase is enhanced in the presence of fibrin and is greater in platelet-rich than in platelet-poor clots. Staphylokinase spares fibrinogen and circulating plasminogen, whereas streptokinase degrades fibrinogen and tPA consumes plasminogen. A major disadvantage of the agent is its immunogenicity, but modification of the molecule has resulted in a less antigenic compound that retains fibrin specificity. Recombinant staphylokinase is undergoing active clinical investigation.

Single-chain urokinase

In plasma, scuPA is mostly inactive, but within the thrombus, it binds to plasminogen, converting it to plasmin. The plasmin digests fibrin, exposing sites to which plasminogen may bind. Single-chain uPA then activates this plasminogen to plasmin, thereby amplifying plasmin generation and producing clot lysis. Unfortunately, the problems that have plagued urokinase production have also affected the development of scuPA as a thrombolytic agent.

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