Brief Review

Thrombolytic therapy

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Thrombolytic therapy represents a new medical approach to the treatment of patients with thromboembolic disease.¹ Streptokinase and urokinase are presently the only two thrombolytic drugs in use. The advantage of thrombolytic agents is that they can dissolve thromboemboli, unlike the more conventional anticoagulant therapy with heparin and coumarin which is capable only of prevention of future clots.² Thrombolytic drugs, therefore, are able to permit the return of blood flow through the affected vessels, reducing pain and possibly the morbidity and mortality associated with vascular occlusion.¹

Anaesthetists are likely to encounter patients who are receiving thrombolytic therapy either in the operating room or in the intensive care unit. It is imperative, therefore, to have an understanding of the basic physiology and pharmacology of thrombolytic drugs as well as some practical insight into their clinical usage.

We will review the pharmacology, mechanisms of action, indication for use, complications and contraindications to therapy with streptokinase and urokinase.

Streptokinase and urokinase

Streptokinase and urokinase are compared in Table I. Although discovered in 1933³ the first intravenous injection of streptokinase was not reported until 1955.⁴ In 1959 it was shown to successfully lyse thrombi that had been experimentally induced in forearm veins of volunteers.⁵ Streptokinase is a foreign protein and therefore is capable of stimulat-

ing allergic reactions in susceptible patients. It is isolated from the broth of group C streptococci. Streptokinase is more widely used than urokinase, being approved for use in pulmonary embolism, deep venous thrombosis, maintenance of patency of vascular access devices and shunts and transmural myocardial infarction.⁶

Urokinase was isolated from human urine by Macfarlane and Pilling in 1946.⁷ Urokinase is non-allergenic, being derived from human protein. However, its cost is more than that of streptokinase and is approved only for pulmonary embolism.⁶

Mechanism of action

These drugs have the ability to activate the body's natural fibrinolytic system. When plasminogen is converted to plasmin, it becomes a proteolytic agent capable of digesting fibrin, fibrinogen, prothrombin and Factors V & VIII. Fresh fibrin clots are lysed with the generation of fibrin degradation products (Figure). Urokinase activates plasminogen directly by peptide bond cleavage at two different sites on the plasminogen molecule. Streptokinase is an indirect activator. Initially it combines with plasminogen to form an activator complex. This complex then converts free plasminogen to plasmin.²

Coagulation abnormalities should return to normal within several hours of discontinuing treatment. Urokinase has a half-life of 16 minutes, while streptokinase has two half-lives. The first is 18 minutes and represents clearance after binding with antistreptokinase antibodies. The second involves the metabolism and excretion of the unbound drug and is not well understood. Streptokinase has a half-life of 83 minutes by this mechanism.⁸

Laboratory monitoring

Laboratory monitoring of fibrinogen, plasminogen and partial thromboplastin time (PTT) does not

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TABLE I Comparison of the features of streptokinase and urokinase

Feature	Streptokinase	Urokinase
Source	Group C streptococci	Human kidney tissue culture; human urine
Molecular weight	47,000 daltons	32,000–54,000 daltons
Half-life	18 minutes	16 minutes
Stability	Room temperature	4° C
Antigenicity	Yes	No
Pyrogenicity	Moderate	Minimal
Indications	Pulmonary embolism, deep-venous thrombosis, vascular access shunts, transmural myocardial infarction, arterial thrombosis	Pulmonary embolism, occluded access shunts
Retail price (\$US) per 250,000 IU (1985)	\$35	\$135

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FIGURE Action of streptokinase and urokinase in achieving thrombolysis. Reprinted with permission.¹

prove reliable in adjusting dosage. Monitoring is useful, however, to determine whether systemic fibrinolysis has been established. The most sensitive test for fibrinolysis is the whole blood euglobulin lysis time, followed by the thrombin time. If these tests are unavailable, then PTT, prothrombin time (PT) or fibrin degradation products should be used. It is important that these tests are performed prior to initiating therapy in order to establish a baseline or control and also to rule out a coagulation defect. A second set of tests should be performed after 3–4 hours of therapy. A prolonged PT, PTT or decreased fibrinogen concentration will ensure that systemic lysis has been established.² It is particularly important to perform coagulation studies early after initiating streptokinase therapy because the dosage regimen varies considerably due to differences in the titre of streptococcal antibodies. For patients with very high levels of antibodies, uroki-

nase or heparin might be more effective. Patients who show no evidence of fibrinolysis with urokinase probably lack sufficient plasminogen substrates. Heparin therapy should be initiated in these patients.

Clinical indications

Thrombolytic agents have been investigated in numerous clinical situations. Many of these trials, however, have been criticized because of a lack of adequate data.⁸ The United States Federal Drug Administration has defined the clinical indications for these drugs (Table II). Streptokinase has been approved for treatment of acute pulmonary embolism, deep venous thrombosis, acute myocardial infarction and occlusion of access shunts and intravascular or cavity catheters. Although under investigation it is presently not approved for retinal vein thrombosis, heart valve obstruction or haemothorax. Urokinase is approved for use in acute pulmonary embolism, occlusion of access shunts and intravascular and cavity catheters. Presently it is not yet approved for vitreous haemorrhage or renal-cortical necrosis.

Pulmonary embolus

One of the earliest uses of thrombolytic agents was in the treatment of pulmonary embolism. Clinical trials conducted by the National Heart, Lung, and Blood Institute in 1973 and 1974 clearly documented the superiority of streptokinase and urokinase as compared with heparin in resolving existing

TABLE II Summary of clinical results in thrombolytic therapy

Condition	Status
Pulmonary embolism	Accelerated resolution of fresh emboli, improvement in angiographic and haemodynamic parameters, possible lower mortality
Deep vein thrombosis	Lyses deep vein thrombosis more often and more completely than heparin, preserves venous valvular function and therefore reduces frequency and severity of postphlebitic syndrome
Peripheral arterial occlusion	Used for lysis of acute arterial thrombi and lysis of arterial emboli, should not be used for arterial emboli originating from the left side of the heart
Myocardial infarction	Does not decrease mortality
Occluded arteriovenous shunts	No controlled studies, should be considered an alternative to surgery
Retinal vessel occlusion	Further studies required before determining efficiency

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Marder VJ. *Ann Intern Med* 1979; 90: 802.

pulmonary emboli. In addition, there was greater improvement in haemodynamic variables (right heart and pulmonary artery pressures) with lytic therapy than with heparin. Unfortunately, at the present time there has been no demonstrable difference in mortality between patients given heparin and those treated with thrombolytics for pulmonary embolism. Many investigators believe, however, that the use of thrombolytics (particularly in cases of recurrent thromboemboli) may prevent or minimize the development of pulmonary hypertension.

Deep-venous thrombosis

The treatment of deep-venous thrombosis has in the past been restricted to the use of heparin. Heparin exerts its anticoagulant effect by enhancing the activity of antithrombin III, an α -globulin that inhibits the activated clotting factors XII α , XI α , X α , IX α and thrombin via binding or their serine residues. Recently, however, streptokinase has been found to be an equally effective and in some ways superior mode of therapy. Kakkar *et al.*¹¹ noted that lysis of deep-venous thrombi in the lower

extremities with streptokinase tended to preserve the anatomy and function of the venous valves more often than did heparin. This observation may eventually prove important in attempts to prevent or reduce the occurrence of chronic venous insufficiency.

Acute myocardial infarction

Angiographic studies have shown that coronary artery thrombosis is present in about 85 per cent of patients with acute transmural infarction. Selective intracoronary infusion of streptokinase early in the evolution of an acute myocardial infarction has resulted in successful recanalization in about 80 per cent of patients.¹² Patients with a recent (less than four to six hours) onset of typical chest pain with ST segment elevation that persists after sublingual nitroglycerin are excellent candidates for this treatment. Reperfusion-associated arrhythmias may occur in as many as 80 per cent of patients given intracoronary streptokinase. The most common are accelerated idioventricular arrhythmias.¹³

Peripheral arterial thrombosis

Although the use of a balloon catheter has simplified the treatment of this vascular emergency, the technique is best suited for the removal of emboli from large calibre arteries and is less effective when the distal arterial tree is involved.¹⁴ The use of thrombolytic treatment in acute arterial thrombosis has been shown to be effective with marked improvement in the vast majority of patients.¹² The advantages of infusing small amounts of thrombolytic drugs directly into the affected area through the arterial catheter positioned adjacent to the thrombus overcomes the limitations and complications of systemic administration.

Regardless of the drug employed, method of infusion or pathology treated, the following factors will influence the success of thrombolytic therapy: (1) thrombi in small or totally occluded vessels are difficult to lyse; (2) lesions greater than seven days old do not usually revolve; (3) massive clots are difficult to lyse; (4) extremes in body temperatures reduce the effectiveness of the fibrinolytic system.⁸

Complications

The use of these agents is associated with a high incidence of complications (Table III). The most

TABLE III Complications of thrombolytic therapy

Condition	Status
Haemorrhage	Overall incidence 30–50% Chance of bleeding increased with systemic administration. Usually at site of venipunctures and arterial cannulation Rarely will produce life-threatening GU, GI or CNS haemorrhage
Allergic reactions	Nausea, vomiting, muscle and skeletal pain, skin rash, headache, itching (incidence 10–15%) Anaphylaxis rare Consider steroid prophylaxis
Fever	Incidence 15–25%
Distal embolization	Due to lysis of arterial thrombi

common complication of fibrinolytic therapy is haemorrhage. Bleeding following fibrinolytic treatment is due to depletion of clotting factors and lysis of recently formed haemostatic plugs.⁶ The incidence of bleeding has been reported to be as high as 30–50 per cent.¹⁵ When administered systemically, haemorrhage requiring transfusion occurs as often as 16 per cent of the time. If given regionally in smaller doses, the bleeding rate is the same as when systemically administered, but is of a minor degree and easily controlled.¹⁶ The risk of haemorrhage increases with the length of infusion and is not related to the degree of systemic fibrinolysis.² Bleeding most often occurs where invasive procedures are performed, such as surgical vascular access, arterial punctures and multiple venipunctures; however, bleeding may also occur in the gastrointestinal and genitourinary systems and intracerebrally.

Mild bleeding, especially from vessel puncture sites in extremities, can often be controlled with mechanical compression. Occasionally, gauze soaked with aminocaproic acid will aid in controlling stubborn oozing. Severe bleeding requires discontinuation of the fibrinolytic therapy. The short half-life allows rapid reversal of the drug effects. Fresh frozen plasma, fresh whole blood or several units of cryoprecipitate should be administered to more rapidly reverse the haemostatic alteration. Although there are no studies documenting its efficiency in this situation, parenteral aminocaproic acid has been recommended to help control bleeding in desperate situations.²

Distal embolization secondary to lysis of arterial thrombi has been reported.¹⁷ It is speculated that this complication occurs when a combination of fresh and old thrombus is present. Rapid lysis of the fresh clot, along with arterial pulsations, may liberate older and more resistant clot fragments. When peripheral embolization occurs, fibrinolytic therapy can be continued as long as the patient is clinically stable and there is no danger of loss of viability of the limb. However, significant occlusion may require surgical intervention.

Other complications include fever and allergic reactions. Up to 25 per cent of patients may have mild temperature elevations with streptokinase while less than 15 per cent of patients receiving urokinase demonstrate temperature elevations.¹⁰ Acetaminophen has been an effective treatment for mild fever. Mild allergic reactions such as urticaria, flushing, nausea, headache and muscle and skeletal pain can occur in patients receiving streptokinase.² Severe allergic reactions with bronchospasm, angioneurotic oedema and hypotension are rare. Minor reactions can be treated with antihistamines at the time of detection. It is not necessary to discontinue use of the agent. The administration of 100 mg hydrocortisone prior to the institution of and every 12–24 hours during streptokinase therapy is useful in preventing these minor reactions.^{2,6}

Extremely rare reactions to streptokinase include diarrhoea, abdominal pain, hepatitis-like reaction, phlebitis and CNS effects such as delirium, depression and psychotic reaction. Cardiovascular complications have included arrhythmias, dyspnoea and tachycardia.⁸

Contraindications to therapy

The major complication associated with thrombolytic therapy is haemorrhage. Awareness of the profound alterations in the body's coagulation cascade caused by the use of these agents should lead to selection of patients in whom the risk of bleeding is minimal.²

Absolute contraindications (Table IV) include a cerebrovascular procedure or process within the preceding two months and an active internal bleeding state. Relative contraindications include those conditions requiring fibrin plugs and strands for normal haemostasis of healing, such as surgery or organ biopsy. The administration of thrombolytic drugs in the postpartum period or following lumbar

TABLE IV Contraindications to fibrinolytic therapy

Condition	Status
Absolute	Active internal bleeding Recent cerebrovascular accident or active neurovascular disease
Relative	Recent lumbar puncture, thoracentesis, major surgery Patients already taking anticoagulant or antiplatelet drugs Patients with active peptic ulcer disease, severe hypertension, malignancy Chronic hepatic or renal disease Heart disease likely to cause cerebral emboli, such as atrial fibrillation

puncture or thoracentesis is contraindicated. No anticoagulant or antiplatelet drugs should be administered while the patient is receiving fibrinolytic therapy. Finally, streptokinase and urokinase should not be given to patients prone to bleeding complications which include those with hypertension or active peptic ulcer disease.¹⁵

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