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THE CURRENT AND FUTURE USE OF THROMBOLYTIC THERAPY

Sol Sherry and Ellen Gustafson

Department of Medicine and Thrombosis Research Center, Temple University School of Medicine, Philadelphia, Pennsylvania 19140

INTRODUCTION

In 1977, the Food and Drug Administration (FDA) approved streptokinase (SK) for the treatment of deep-vein thrombosis and pulmonary embolism and urokinase (UK) for the treatment of pulmonary embolism. Three years later, the FDA, in conjunction with the National Institutes of Health (NIH), sponsored a consensus development conference on these thrombolytic agents (1). After reviewing the data, the panel issued a strong positive statement encouraging physicians to employ these plasminogen activators in the management of proximal deep-vein thrombosis and the more severe forms of pulmonary embolism. This recommendation has resulted in a surge of interest in thrombolytic therapy with the following result: (*a*) increased acceptance of streptokinase and urokinase therapy for the indications previously noted; (*b*) expanded indications for their use; (*c*) application of new techniques and dosage schedules for their administration; and (*d*) development of new thrombolytic agents.

This review provides an update on the current state of the clinical use of thrombolytic agents and their future expectations.

GENERAL ASPECTS

Primary Mechanism for Thrombolysis

The rationale for using plasminogen activators for therapeutic thrombolysis is based on the evidence that the most sensitive mechanism for thrombolysis is the activation of fibrin-bound plasminogen to fibrin-bound plasmin, the latter then acting on its substrate in a relatively inhibitor-free environment (2, 3). Fun-

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damental to an understanding of the special fibrinolytic properties of the plasminogen-plasmin system is that in vivo plasminogen exists in two phases, plasma or soluble-phase plasminogen and fibrin-bound or gel-phase plasminogen, with the plasminogen-plasmin system operating differently in each phase.

Plasminogen, the inactive precursor of the proteolytic enzyme plasmin, is a normal circulating constituent in plasma (its concentration in plasma is analogous to that of prothrombin) and possesses several binding sites for fibrin, the primary one having a very high affinity constant (3, 4); during clotting, approximately 5% of the surrounding plasma plasminogen becomes bound to fibrin and at a site that also serves as the major binding site for α_2-antiplasmin, the immediate, stoichiometric, and irreversible inhibitor of plasmin. In addition, evidence exists that fibrin enhances the rate of activation of plasminogen by plasminogen activators and that there are specific receptor sites on fibrin for plasminogen activators (4). Thus, when a plasminogen activator is in circulation and comes in contact with fibrin, activation of fibrin-bound or gel-phase plasminogen occurs; this produces selective fibrinolysis. Here there are no competing substrates for the action of fibrin-bound plasmin; the latter's action is carried out in a relatively inhibitor-free environment (the affinity of the fibrin-bound plasmin cannot be overcome by its affinity for α_2-antiplasmin); and fibrinolysis proceeds without any evidences of systemic proteolysis. These molecular events provide the rationale for the use of plasminogen activators rather than plasmin (or other proteolytic enzymes) for therapeutic thrombolysis and, more recently, for the development of plasminogen activators more specific for fibrin.

During streptokinase or urokinase therapy, there is also activation of plasma or soluble-phase plasminogen in the circulating blood and this leads to the appearance of free plasmin; the latter degrades fibrinogen, blood-clotting factors V and VIII, and some components of complement. While this action is controlled and dampened by various checks and balances, primarily through the action of such major inhibitors as α_2-antiplasmin and α_2-macroglobulin (slow and non-stoichiometric), there is evidence of considerable fibrinogen proteolysis, with the appearance of significant amounts of breakdown products. The resulting hypofibrinogenemia, impairment of platelet function (fibrinogen is necessary for normal platelet function) and the anticoagulant properties of fibrinogen breakdown products lead to an impaired hemostatic mechanism; this increases the risk of a bleeding episode, the major complication of thrombolytic therapy.

Plasminogen Activators in Clinical Practice

STREPTOKINASE Streptokinase (SK) is the first of the plasminogen activators introduced into clinical medicine, originally for the lysis of extravascular

deposits of fibrin and fibrin coagula, and later for intravascular thrombolysis (5, 6). At present, its approved indications are for the treatment of deep-vein thrombosis, pulmonary embolism, arterial thrombosis and embolism, coronary thrombosis (by intracoronary perfusion), and for the lysis of clotted arteriovenous cannulae (dialysis shunts, for example).

SK is produced from cultures of Lancefield Group C β hemolytic streptococci and has a molecular weight of 47,000 daltons. SK does not directly cleave plasminogen but activates plasminogen indirectly via the formation of an intermediate. The intermediate, a stoichiometric 1:1 complex of human plasminogen or plasmin and SK, then converts plasminogen into active plasmin (7).

In the utilization of streptokinase for therapeutic purposes, variable amounts of circulating antistreptokinase antibody, the consequence of previous streptococcal infections, must be overcome. The cumbersome dose titrations employed in the past to determine the amount of streptokinase required to neutralize such antibodies are no longer performed. Clinical experience with large numbers of patients has shown that a loading dose of 250,000 units given intravenously is sufficient to overcome the antibody level in 90–95% of patients and to initiate a thrombolytic state (8). The exceptions are those patients who have been treated recently with streptokinase, who have had a hemolytic streptococcal infection within the previous six months, or who have maintained a high antibody level.

The antigenic response to SK has been well studied. Antibody titers may rise even during the first day and peak in very high titers from day 7–10. High titers persist for three months and then slowly decline. By seven months after a course of therapy, an initial loading dose of 250,000 units is generally sufficient for initiating another course of therapy. In vivo, SK has two half lives: a rapid one of 16 minutes, which represents antibody complexing and its removal, and a slower one of about 83 minutes, which represents the biologic half life of this protein, its complex with plasminogen or plasmin, and their degradation products (9). However, the half life of the active moieties (free streptokinase and the activator complex) is shorter than the latter, although its duration has not yet been defined.

As noted previously, the administration of streptokinase results in the activation of both plasma plasminogen and thrombus plasminogen; the latter action is primarily responsible for thrombolysis, while the former, which also occurs rapidly and extensively, results in a transient state of hyperplasminemia. The level of this hyperplasminemia and its duration depends upon the rate of plasminogen activation, the concentration of α_2-antiplasmin (normally there is sufficient α_2-antiplasmin to inactivate about half of all the plasmin that can be formed from plasma plasminogen), the rate of inactivation of plasmin by the slower nonstoichiometric and progressive but reversible inhibitor complex formed with α_2-macroglobuin, and the rate of clearance of plasmin by the

reticuloendothelial system. Thus, the state of hyperplasminemia and its effects vary considerably among patients and are primarily observed early during the therapy, when plasminogen is being rapidly activated (first few hours). Subsequently, when plasma plasminogen has been reduced to near zero levels, plasmin activity progressively declines and disappears, despite the continuation of the streptokinase infusion.

During the period of brisk hyperplasminemia, which is usually well tolerated by the patient, most of the fibrinogen is partially degraded; fragment X (a poorly clottable fibrinogen derivative with strong antithrombin activity) appears early, but later there is a progressive appearance of such incoagulable fragments as Y, D, and E, which, with the exception of the latter, are inhibitors of fibrin polymerization. In addition to the effects of fibrinogenolysis on both the coagulation mechanism and the ability of platelets to aggregate normally, there is also a partial degradation of factors V and VIII; all these changes induce a hemostatic defect that resolves slowly as the therapy is continued. This aberration, and the dissolution of fibrin previously laid down at sites of invasive procedures, are responsible for the increased risk of bleeding.

While the activation of plasma plasminogen is a hazard of therapy, it probably also contributes to its success: the induced hemostatic defect inhibits new fibrin formation at the thrombotic site and circulating plasmin may augment the process of thrombolysis; activation of plasma plasminogen perfusing a clot could also contribute to this phenomenon.

UROKINASE Urokinase (UK), currently approved for the treatment of pulmonary embolism and coronary thrombosis (by intracoronary perfusion) and for intravenous catheter clearance (central venous lines, for example), is presently isolated and purified either from human fetal kidney cultures or from human urine; it exists in two forms whose molecular weights are 54,000 and 31,600 daltons. The former is believed to be the native form, the latter an active fragment. UK, an active protease, directly cleaves plasminogen to plasmin. Of the two forms of plasminogen (10), activation of lys-plasminogen proceeds more rapidly than with glu-plasminogen. Interestingly, while it is a native human plasminogen activator, UK is different from the activator(s) appearing in plasma following stimulation of the intrinsic or extrinsic mechanisms of fibrinolysis (11); this suggests that the urinary source of urokinase is in local production in the kidney rather than in excretion from plasma. Although there are no antibodies to overcome with urokinase as there are with streptokinase, nevertheless plasma inhibitors to urokinase and a rapid rate of clearance require that a loading dose be given when the agent is infused systemically; the most frequently used loading dose to initiate a thrombolytic state with urokinase, comparable to that achieved with SK, is 2,000 units per pound of body weight. Since the methods of standardizing urokinase and streptokinase are different,

their units are not the same; in practice, the in vivo activity of approximately three units of UK is comparable to one unit of SK. The half-life of UK in vivo has been estimated at 14 ± 6 minutes (12).

UK has several theoretical advantages as a thrombolytic agent in clinical practice: (*a*) it is non-antigenic and its use is free of allergic reactions; (*b*) no anti-UK antibodies are present to interfere with drug action, although a variability exists in its rates of inactivation and clearance; and (*c*) compared to SK it has a greater affinity for fibrin-bound plasminogen than for plasma plasminogen. This increased affinity for fibrin-bound plasminogen allows clot lysis to occur with a milder hemostatic defect (13). Nevertheless, in studies comparing UK with SK that were designed to produce approximately equivalent levels of circulating plasminogen activator activity (14) and are currently being used in practice, no significant differences in clinical efficacy were observed, nor were there significant differences in the incidence of hemorrhagic complications (the initiation of a bleeding complication is most frequently due to the lysis of a hemostatic plug at the site of a recent invasive procedure and not to the hematologic changes, while the latter is more responsible for the duration and severity of the bleeding episode). Considering these observations, the much lower cost of SK has made it the more favored therapeutic agent in clinical medicine.

Factors Regulating In Vivo Thrombolysis

Once a thrombolytic state is established in vivo with either UK or SK, there is little correlation between the level of circulating plasma clot–dissolving activity and the rate or extent of thrombolysis (13). The latter appears to be dependent primarily on local factors in and around the thrombus rather than on measurable changes in the circulation. These factors include: (*a*) the accessibility of the activator to the thrombus; (*b*) the surface area of the clot exposed to the plasminogen activator; (*c*) the concentration of fibrin-bound plasminogen within the clot; (*d*) the activator concentration surrounding the thrombus; and (*e*) the age of the clot [fresh clots dissolve more readily than older ones (15)]. As a result, at present there are no useful tests for regulating dosage of the agents or rates of administration so as to maximize the speed of resolution of a thrombus; modifications of commonly employed regimens (see below) have been empirical, including attempts to reinforce the plasminogen content of thrombi (16). No evidence exists that any of these modifications has improved the therapeutic results.

Monitoring of Therapy

With the accumulation of evidence that the hematologic findings associated with thrombolytic therapy correlate poorly with either the clinical result or in predicting bleeding complications (13), monitoring of these changes during

therapy no longer appears necessary or useful. Rather, during treatment one seeks only evidence that sufficient plasminogen activator is present in the circulation to activate plasminogen. At present, when SK or UK are administered systemically, it is recommended that three to four hours following the onset of the infusion a blood sample be obtained that demonstrates a prolongation of the partial thromboplastin time, a reduction in plasma fibrinogen, the appearance of increased levels of fibrinogen-fibrin degradation products, or a shortening of the euglobulin lysis time. If these do not occur, the patient is probably resistant to the activator; under these circumstances, one either switches to another activator or discontinues the treatment and initiates anticoagulant therapy instead.

With local perfusions, where lower doses of SK or UK are administered, the systemic hematological changes are milder, but one can usually demonstrate a reduction in plasma fibrinogen even though the partial thromboplastin time may remain unaffected. (The commonly employed clinical laboratory determination of fibrinogen is the most sensitive test for demonstrating plasma-plasminogen activation because it measures the totality of normal and slowly clottable fibrinogen as well as the antithrombin and antipolymerizing action of fibrinogen degradation products.)

Adverse Reactions

ALLERGIC REACTIONS Allergic reactions have been observed in 1–2% of patients receiving streptokinase. These may include rash, urticaria, angioneurotic edema, bronchospasm, and anaphylactoid reaction. Most of these can be prevented by premedicating the patient with intravenously administered hydrocortisone (repeatable at 12-hour intervals during prolonged infusions). In the unusual instance of an anaphylactoid reaction, therapy should be stopped and the patient treated in the usual manner for such reactions.

FEVER A febrile episode is not uncommon following streptokinase administration. The incidence of such febrile episodes (usually mild) can be reduced to less than 5% by hydrocortisone premedication. With urokinase, fevers may also occur in 1–2% of patients, although the mechanism is obscure. Allergic reactions are not seen with urokinase.

BLEEDING COMPLICATIONS Bleeding is the major and most serious complication associated with thrombolytic therapy. The incidence has been variable and is dependent upon the investigator's definition of bleeding; some have reported all bleeding episodes, including minor cutdown or venipuncture oozing, others only transfusion-dependent episodes, and some only life-threatening episodes.

Attention to proper techniques and patient selection are critical factors in determining the incidence of bleeding. Bleeding can be expected to be initiated

in a large percentage of patients with a recent invasive procedure; this is due to the lysis of a fibrin-stabilized hemostatic plug. However, this bleeding usually can be prevented by careful planning or controlled by pressure dressings. Severe bleeds requiring systemic therapy (cryoprecipitate, fresh-frozen plasma, or whole blood) occur in about 5% of cases. While most of these are at sites of known vascular injury, others are not (gastrointestinal, retroperitoneal or cerebral). The lowest incidence of severe bleeds, less than 1%, has been reported in patients receiving a single bolus injection of SK (high-dose, brief-duration therapy) for the lysis of a coronary thrombus (17).

Contraindications

Patient selection is very important if one is to minimize bleeding complications. Absolute contraindications include: (*a*) active bleeding lesions; (*b*) the presence of vascular intracranial disorders, such as cerebrovascular accident or a transient cerebral ischemic episode within the previous two months, cerebral tumors, or a cerebral arterio-venous malformation; and (*c*) cardio-pulmonary resuscitation because of underlying chest trauma.

Relative contraindications include: (*a*) age over 70; (*b*) large abrasive wounds, fractures, major surgery, or deep-closed biopsies within the previous ten-day period; (*c*) severe or accelerated hypertension (diastolic pressures greater than 110 mm Hg); and (*d*) any known increased bleeding risk, such as the presence of a constitutional or acquired coagulation or platelet defect, severe liver failure, or advanced uremia.

Not sufficiently stressed in the literature is the apparent synergistic action of heparin anticoagulation in increasing the bleeding incidence in patients receiving SK or UK therapy. In one study, the incidence of bleeding with low-dose SK (approximately one-tenth the usual dose) plus full-dose heparin therapy was as great as that observed with high-dose SK alone (18); in another study, the combination of low-dose SK with low-dose heparin was worse than high-dose SK alone (19). And while a low incidence of bleeding complications (0.8%) has been reported for patients receiving high-dose, short-duration intravenously administered SK (1.0–1.5 million units) for acute myocardial infarction (17), a recent study involving a smaller dose of SK (750,000 units) combined with high-dose heparin therapy had a 12.3% incidence of serious bleeding complications, including two intracerebral bleeds (20). The simultaneous use of heparin with SK or UK therapy should be avoided whenever possible.

THROMBOLYTIC THERAPY FOR SPECIFIC CLINICAL STATES

Deep-Vein Thrombosis

RATIONALE While anticoagulation is the mainstay of therapy for a deep-vein thrombosis, it serves only as a secondary preventive measure; it slows or stops

the underlying thrombotic process and in so doing inhibits extension of the venous thrombosis and decreases the likelihood of pulmonary embolism or its recurrence. However, anticoagulation has no acute demonstrable effect on the original thrombus. The natural history of such thrombi is to undergo organization and subsequent recanalization but with loss of normal venous valvular function. Serial venographic studies carried out during the first week in patients treated with heparin following an attack of proximal deep-vein thrombophlebitis have shown that complete resolution of the venous thrombosis can be expected to occur in only 10% or less of patients and some resolution may be evident in approximately another 15%, but the remainder (75%) show either no resolution or some progression of the underlying process (21). Pathologic and radiologic studies have shown that large venous thrombi that do not undergo rapid resolution are organized and recanalized, but the new channel contains no valves or, where valves remain, they are functionally inadequate because of cicatricial changes and anatomic disfiguration. Thus, most patients are left with persistent venous hypertension in the affected extremity (22, 23), remain symptomatic (pain, swelling), and are at permanent high risk for recurrent thrombophlebitis and a disabling post-phlebitic insufficiency syndrome. In a study by Elliott et al (22), 21 of 25 patients treated with adequate anticoagulation alone for proximal thrombophlebitis were available for two-year follow-up studies; 19 were still symptomatic, with four having developed venous claudication and one suffering from venous ulcers. In Arnesen's study, which followed patients for an average of 6.5 years, similar results were obtained (23). Of the 18 patients in the heparin group available for follow-up, none had a normal venogram, only six were asymptomatic, and three of the 12 symptomatic patients had developed a full-blown post-phlebitic insufficiency syndrome.

RESULTS The consequences described above can be avoided if blood flow is restored to normal before venous valvular function is seriously impaired, and this can be accomplished by thrombolytic therapy in a majority of cases (15), particularly when the lesion is less than 72 hours old. Not only has this therapy avoided many of the late complications observed when anticoagulation is used as the only form of therapy (21), but the immediate effect has been a more rapid improvement in the clinical picture (24). Thus, thrombolytic therapy, when used properly in appropriately selected cases (25, 26) and in tandem with anticoagulation, offers the physician a significant advance in the therapy of proximal deep-vein thrombosis, including socioeconomic considerations (27).

INDICATIONS At present thrombolytic therapy is recommended for all cases of adequately documented (usually by venography) proximal deep-vein thrombosis of the upper and lower extremities, provided that the benefit-risk ratio favors its use.

RECOMMENDED METHOD OF ADMINISTRATION AND DOSAGE Thrombolytic therapy for deep-vein thrombosis is most commonly carried out by a sustained intravenous infusion via an infusion pump into an antecubital vein. The recommended dosage for streptokinase is a loading dose of 250,000 units given over a 30-minute period, followed by a sustaining infusion of 100,000 units per hour. The therapy is continued for periods of up to 72 hours depending on the clinical result. The objective is to restore blood flow to normal as gauged by non-invasive techniques and to discontinue therapy when this is achieved. Heparinization is then instituted to prevent recurrence. Guidelines for this form of therapy have been published (25, 26).

As yet, urokinase has not been approved for deep-vein thrombosis, but it has been used successfully for this purpose with currently recommended dosages, i.e. a loading dose of 2,000 units per pound of body weight given intravenously over a 10-minute period, followed by a sustaining infusion of 2000 units per pound of body weight per hour until blood flow has been restored (28, 29).

Acute Pulmonary Embolism

RATIONALE The natural history of pulmonary embolism in anticoagulated patients is not very dissimilar from that of the venous thrombi from which they arise (21). This is based on the following evidence: (*a*) heparin does not acutely affect the pulmonary hypertension that frequently occurs with a large embolic episode and, although the hypertension moderates with time, increased pulmonary vascular resistance and pulmonary hypertension persist, along with a reduction in the total pulmonary capillary blood volume; (*b*) perfusion defects are still present in a significant percentage of cases (25–30%) when studied serially over several years; and (*c*) pathological observations reveal that pulmonary emboli frequently undergo organization and recanalization, ultimately leaving fibrous webs and bands as hallmarks of previous emboli. To prevent these late consequences, which can affect the long-term prognosis, rapid restoration of blood flow following a large embolic episode is required.

RESULTS Successful lysis of acute pulmonary emboli can be achieved in the majority of cases (13, 14), and the acute clinical effects are considerably better than those observed with anticoagulation alone (30, 31), as are the late consequences (32).

INDICATIONS Barring significant contraindications, thrombolytic therapy is recommended for any of the following conditions: (*a*) pulmonary embolism with evidence of acute pulmonary hypertension; (*b*) pulmonary embolism associated with protracted shock; and (*c*) pulmonary embolism with a perfusion defect (single or multiple) equivalent to one lobe or more.

RECOMMENDED METHOD OF ADMINISTRATION AND DOSAGE Once the diagnosis is established by objective methods, treatment is carried out by an intravenous infusion as for deep-vein thrombosis except that the duration of therapy with streptokinase is 24 hours; with urokinase it is 12 hours. However, if the pulmonary artery pressure is being monitored or a pulmonary angiogram is performed, the infusion can be administered directly into the pulmonary artery; under these circumstances, a loading dose of SK or UK is unnecessary. While the results of direct perfusion into the pulmonary artery are very impressive (33), they are not very different from those achieved using the intravenous route.

Arterial Thrombosis and Embolism

RATIONALE Rapid removal of an acute thrombotic or embolic arterial obstruction, if feasible, has always been considered a primary objective of therapy so as to avoid tissue necrosis or permanent impairment of the circulation. Thrombolytic therapy provides either an alternative or an adjunct to surgery.

RESULTS AND INDICATIONS When used in the same manner as for venous thrombosis or pulmonary embolism, thrombolytic therapy produces results on the arterial side similar to those achieved in the lesser circulation (15, 34). Also, as on the venous side, emboli are more readily lysed than thrombi (34). Nevertheless, because many immediate successful surgical techniques are available for managing acute arterial thrombo-embolic problems, especially in the extremities, the indications for the use of systemic thrombolytic therapy as currently practiced is usually restricted to situations where an operative procedure is refused or is not likely to be tolerated or where the lesion is not accessible, e.g. in more distal vessels of the extremities.

Recently, however, a number of investigators (35–39) have extended the indications and usefulness of thrombolytic therapy by passing catheters to the immediate proximity of an acute thrombus or embolus and locally perfusing the vessel with a thrombolytic agent. The advantages of such an approach are: (*a*) delivery of the agent to the intended site is assured; (*b*) higher local concentrations of these activators are achieved with lower dosage schedules, thus maximizing rates of clot lysis while minimizing systemic effects and bleeding complications; and (*c*) the duration of therapy can be shortened and effectively tailored to the desired therapeutic objective with the aid of serial angiographic studies or suitable alternatives (oscillometry, for example). This approach is now being used for all lesions accessible to local perfusion; it has allowed the vascular surgeon to employ both surgical techniques and lytic therapy to best advantage in the total management of complex problems (40), and has allowed the interventional radiologist to employ both thrombolysis and percutaneous

transluminal balloon angioplasty for the total management of a thrombosed atherosclerotic vessel (41).

As with venous thrombo-emboli, the age of the clot is an important determinant in the success of lysis. While several investigators (34, 42) have reported lysing older peripheral arterial thrombotic occlusions (several weeks to several months in duration) with relief of ischemic symptoms (intermittent claudication, etc), the success rate progressively declines with age of the thrombus; the duration of therapy to achieve reperfusion is also lengthened, and bleeding complications are increased. Consequently, the value of thrombolytic therapy for chronic peripheral arterial occlusions by local perfusion of the affected vessel remains controversial.

RECOMMENDED DOSAGE FOR LOCAL PERFUSION Many dosage regimens have been used; they range from 5,000–50,000 units per hour for streptokinase and from 15,000–200,000 units per hour for urokinase. Since there are no reports of studies with dosage as the only variable, the superiority of one dosage schedule over another has not been established. Higher dosages may be expected to produce more rapid rates of lysis but with more extensive hematological changes; lower doses are usually given with larger amounts of heparin and may be subject to a higher incidence of bleeding.

Acute Myocardial Infarction

RATIONALE The amount of myocardium that becomes necrotic with acute myocardial infarction determines the acute outcome and long-term prognosis. Major efforts in the past to develop methods for substantially reducing the size of myocardial infarction have not been very successful (43). Coronary thrombolysis is a promising treatment for this purpose, since an actue thrombus at the proximal border of an atherosclerotic obstruction usually underlies myocardial infarction (44, 45). While the use of fibrinolytic therapy is predicated on its potential for lysing an acutely obstructing thrombus and restoring blood flow, other actions may play a salutory role in this condition, as follows: (*a*) reduction in plasma viscosity consequent to the degradation of fibrinogen, and (*b*) improved flow through the lysis of platelet-fibrin thrombo-emboli in the microcirculation of the ischemic area (46). The latter effect could salvage myocardium otherwise destined to infarct and/or reduce the electrical instability of the marginal zone of ischemia.

METHODS OF ADMINISTRATION AND RESULTS Three forms of therapy with plasminogen activators have been investigated for salvaging myocardium in patients undergoing a myocardial infarction: (*a*) sustained intravenous infusion for 24 hours, (*b*) intracoronary perfusion, and (*c*) high-dose, brief-duration (one hour) intravenous infusion.

Sustained 24-hour intravenous infusion Sustained 24-hour intravenous infusion is the original form of therapy introduced for the treatment of acute myocardial infarction with streptokinase (6) and was employed in a series of trials begun in the mid-sixties and continued throughout the seventies (47). While the dosage and the duration of therapy varied, most of the studies used a regimen similar to that described for pulmonary embolism.

Many of these trials, including the well-designed European Cooperative Study (48), claimed a significant reduction in mortality compared to untreated controls. A recent review of the total data (47) suggests that the therapy probably was associated with a reduction in mortality of approximately 20%. However, the cardiological community in the United States either never took these studies seriously or expressed only passing interest (49). The reasons for this were:

1. The importance of coronary thrombosis as the precipitating factor in acute myocardial infarction, even when the latter was transmural, was minimized on the basis of a study (50) that was readily accepted by leading academic cardiologists, even though most of the information on this subject still indicated a high association (51). And when coronary thrombosis was present at autopsy, it was relegated to a secondary event of little or no pathogenic significance (50).
2. To satisfy the biometricians and cardiologists, trials had to be conducted in patients with a proven myocardial infarction (evolutionary changes in the electrocardiogram and elevated enzyme levels). Thus, many studies were undertaken only in patients whose zone of infarction was already completed or almost so. Under these circumstances, successful lysis of a coronary thrombus could only be expected to have limited goals, i.e. to prevent further extension of an already fairly fully developed infarct or to reduce the myocardial irritability arising from the marginal zone of ischemia.
3. The advent of coronary care units, with their constant monitoring of patients and their aggressive management of early rhythm or hemodynamic disturbances, not only reduced mortality to a point where trial numbers would have to be expanded greatly to prove a significant reduction in mortality, but also could have salvaged the same patients likely to be helped by the lysis of a thrombus.
4. The multiple invasive procedures carried out in coronary care units significantly enhanced the risk of bleeding associated with thrombolytic therapy, and it became increasing dangerous to treat patients by protracted systemic infusions (52).
5. Studies on infarct size reduction, which could have served as an alternative to mortality trials and allowed for an answer using much fewer patients, could not be carried out because of the lack of an acceptable method for measuring infarct size in the living patients.

Local intracoronary perfusion With the demonstration that (*a*) coronary catheterization, angiography, and ventriculography could be carried out relatively safely in patients during the first few hours of an evolving myocardial infarction, and (*b*) an occluding thrombus was responsible for the lack of perfusion of the jeopardized mycardium, the opportunity was provided to treat such patients by direct local perfusion of the obstructed vessel before extensive infarction had taken place, and to evaluate the results.

Since the initial encouraging report by Rentrop (53), many investigators, as noted in a recent review (54), have substantiated his findings. On the average, in 75% (range 62–95%) of the patients studied, the obstructed coronary vessel was successfully recanalized by local streptokinase perfusion, usually within 20–30 minutes of the introduction of the agent into the obstructed artery. While the proven benefits of such therapy are still being debated, considerable evidence has accumulated that this therapy, when successful, does reduce infarct size (55–58); a recent trial also has claimed a significant reduction in mortality (59).

The dosages employed by cardiologists for perfusion of the obstructed coronary artery have ranged from 2,000–8,000 units per minute, usually given over a one-hour period (total dosage has varied between 100,000–500,000 units). Because of the insertion of a catheter (femoral artery approach), the patients have received heparin along with the streptokinase. Based on a survey of the current literature (54), the bleeding complication rate using this form of therapy has been 4.8%. The other significant problem encountered has been a 16% incidence [range 5–25% (54)] of recurrent thrombosis in the previously affected artery. Consequently, following thrombosis, a number of institutions employ coronary by-pass surgery or transluminal balloon angioplasty when a high degree of stenosis underlies the site of previous thrombosis (60).

Almost all studies on intracoronary perfusion have been conducted with SK, but in a recent trial the local perfusion of UK produced equivalent results to those observed with SK (61).

High-dose, brief-duration intravenous infusion of SK In order to make streptokinase therapy for acute evolving myocardial infarction available to a much larger number of patients (many hospitals do not have catherization laboratories or trained personnel available at all times) without the morbidity associated with coronary catherization and without the delays in initiating treatment (coronary catheterization and angiography may take up to two hours), attempts are now underway to reproduce the results of intracoronary thrombolysis by high-dose, brief-duration intravenously administered streptokinase. The objective of the high dose is to flood the circulation with sufficient streptokinase to produce rapid thrombolysis of a coronary thrombus. Thus, doses of 500,000–1,500,000 units of SK have been infused over an hour's time, with the latter dose being the most popular. The rationale for the brief duration is to allow for

early recovery of the hemostatic mechanism, thus minimizing the likelihood of a serious or protracted bleeding episode.

The initial results have been very encouraging (62–66): angiographic studies have demonstrated a reperfusion rate of 44–60% (average 51%), a bleeding complication rate of only 0.8%, and an average reocclusion rate of 18% (range 9–29%) (54).

More recent studies have reported higher rates of reperfusion (67, 68); however, these regimens are sufficiently different in design [duration of therapy (67) or simultaneous use of high-dose heparin therapy with a very significant increase in bleeding episodes (68)] to consider these studies independently of the others.

As with intracoronary perfusion, evidence is accumulating that high-dose, brief-duration, intravenously administered SK reduces infarct size (54), while the first major randomized trial evaluating mortality with this form of therapy will be completed soon (R. Schroder, personal communication).

Clotted Intravenous Catheters and Shunts

Streptokinase has been approved and has been used successfully for the treatment of arteriovenous cannula occlusion. After failure of other methods to relieve the thrombotic occlusion, 250,000 units of SK in 2 ml of an intravenous solution are injected into each occluded limb of the cannula; the cannula limbs are clamped off for two hours, the lysed contents are then aspirated, the cannula limbs are flushed, and the clamps are removed.

Urokinase has been approved and both UK (69) and SK (70) have been used successfully for clearing various types (intravenous alimentation catheters and Hickman catheters, for example) of occluded central venous lines. In this situation, small amounts of UK or SK are injected into the catheter in an amount equal to the volume of the catheter and the catheter is clamped distally. After a period of time (between five minutes and an hour), the catheter is aspirated of its contents and flushed.

Miscellaneous Uses of Thrombolytic Therapy

UNSTABLE ANGINA Since a fair percentage of patients with unstable angina reveal evidence of partially obstructing thrombi during coronary catheterization, several investigators have reported on the potential value of SK therapy either intravenously (71) or by intracoronary perfusion (72) for this condition. Further investigation of thrombolytic therapy for this entity is indicated.

CEREBRAL VENOUS SINUS THROMBOSIS Because of the high mortality rate of cerebral venous sinus thrombosis and the lack of any effective therapy for this condition, attempts have been made by several investigators to treat such

patients with thrombolytic therapy (73, 74). While the reports are encouraging, the numbers of patients are small and the investigation still in an early stage.

PROSTHETIC VALVES Thrombotic occlusion of a prosthetic valve is an acute catastrophe that could lend itself to thrombolytic therapy as an alternative to emergency surgery. There are several reports on the successful use of SK and UK for this condition (75, 76).

NEW THROMBOLYTIC AGENTS CURRENTLY UNDER CLINICAL INVESTIGATION

Tissue Plasminogen Activator

As previously noted, the activation of plasma plasminogen by streptokinase or urokinase in the circulating blood usually leads to a significant hemostatic defect (fibrinogen reduced, fibrinogen breakdown products increased, impaired platelet function, and other conditions). In contrast, the activator made by endothelial cells, fibroblasts, tumor cells, etc, utilizes fibrin as a co-factor for the activation of plasminogen. Thus, when this type of human activator, referred to as tissue-type plasminogn activator (TPA), is introduced into the blood stream, minor hemostatic abnormalities ensue; its activity is restricted primarily to activation of the fibrin-bound plasminogen, the most sensitive mechanism for thrombolysis. The theoretical advantage of TPA and TPA-like agents is that they could greatly increase the safety of thrombolytic therapy and ultimately change the practice habits of all physicians, i.e. to use thrombolytic therapy initially for all acute thrombo-embolic events followed by anticoagulation to prevent a recurrence. Currently, an extensive investigation is underway to evaluate TPA. Originally the material was obtained in tissue culture from a human melanoma cell line; preliminary studies on the lysis of venous and coronary thrombi with this preparation have been encouraging (77, 78). The agent is now being made in tissue culture by recombinant DNA techniques (rTPA) utilizing a mammalian cell line, and this material is undergoing clinical study (79).

Acylated Streptokinase-Plasminogen Activator Complex

Another development in the use of thrombolytic therapy involves the acylation of the streptokinase-plasminogen activator complex; this inactivates the SK activator so that, when the acylated streptokinase-plasminogen activator complex is introduced into the blood stream, no hemostatic abnormalities are produced. However, after the acylated compound binds to fibrin, deacylation takes place; this releases the original activator complex so as to activate the plasminogen bound to fibrin. Although animal studies with such preparations

have been very encouraging (80), recent observations in man indicate that the presently used substances are deacylating in the general circulation and induce a hemostatic defect (81, 82).

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