review
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CURRENT CONCEPTS IN CORONARY THROMBOLYSIS

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ABSTRACT

Thrombolytic therapy has become standard care in treating acute myocardial infarction. Fibrinolytic drugs such as streptokinase, APSAC and urokinase are non fibrin specific, and induce systemic activation of the fibrinolytic process, while t-PA and prourokinase are fibrin specific since they are able to activate mainly fibrin bound plasminogen. Both groups of thrombolytics exert different and opposing effects on the hemostatic balance: indeed, they have antithrombotic as well as prothrombotic properties, and this may be important for explaining therapeutic failures or reocclusions. New strategies have been considered or are under investigation for further improving the already excellent efficacy of thrombolytic treatment in myocardial infarction: combined administration of fibrinolytic agents, thrombus-targeted thrombolytic drugs, association with other drugs both effective and ineffective on the hemostatic process. At present, however, the first priority still seems to be a continuing effort to increase the percentage of patients treated with thrombolytics, since the benefits of this therapy have already been clearly demonstrated.

Key words: thrombolysis, myocardial infarction, antithrombotic effects, prothrombotic effects, fibrin specificity

In the past 10 years, thrombolytics have become standard therapy for acute myocardial infarction. Although the ability of streptokinase to lyse clots was first recognized in the 1930s, thrombolytic therapy was not used to treat acute myocardial infarction until the early 1980s, when the importance of thrombosis in the pathogenesis of acute infarction was fully recognized. Since then different studies have investigated the complex problems related to fibrinolytic treatment in acute myocardial infarction: choice of drug, dose, the results in terms of reperfusion and survival, the incidence of reocclusion, association with other drugs and side effects. The great effort directed to this area has stimulated the search for new drugs and, more importantly, has dramatically increased our knowledge about old and new thrombolytics.

Furthermore, widespread use of these drugs has allowed clarification of their different effects on the hemostatic balance; some of them are fibrin specific, that is they activate mainly fibrin-bound plasminogen, while others are able to induce systemic activation of the fibrinolytic process.

The aim of this review is to describe the characteristics of the main thrombolytic agents, to illustrate their different and opposing effects on the hemostatic system, and to discuss implications for further research.

Main thrombolytic drugs

Table 1 outlines the major features of the thrombolytic agents currently in use.

Non fibrin specific drugs

Streptokinase

This thrombolytic agent is a single chain protein containing 415 amino acids, and having a molecular weight of 47 kD; it is produced by β-hemolytic strains of Streptococcus.[1]

Streptokinase is a non enzyme protein which indirectly activates the fibrinolytic system by forming a 1:1 stoichiometric complex with plasminogen. This streptokinase-plasminogen activator complex then converts non complexed plasminogen to plasmin. Streptokinase adminis-

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tration provokes a decrease in plasma levels of plasminogen, α2-antiplasmin, fibrinogen, factor V and factor VIII, and an increase in plasma levels of fibrin(ogen) degradation products (FDP); it is the typical example of systemic activation of fibrinolysis.

Almost everyone has some level of circulating antibodies to streptokinase as a consequence of previous infections by β-hemolytic strains of Streptococcus. After streptokinase administration such antibodies dramatically increase their levels in plasma, or become detectable if previously absent. Antibody titer progressively increases for several weeks and then slowly decreases, but it may persist for years at levels higher than the basal value.[2-4] Therefore in the case of reocclusion a second dose of streptokinase is likely to be effective only when administered within 48 hours of the first one; after that time other thrombolytics have to be used.[5-8] In spite of the large incidence of such antibodies, allergic reactions associated with streptokinase administration are very rare.

Hypotension as a result of thrombolytic therapy is best described for streptokinase. This effect is probably the result of plasmin induced kallikrein activation and release of bradykinin,[9] or it could be due to more complex mechanisms involving *platelet activating factor.*[10] In any case, although patients with low systolic blood pressure during streptokinase infusion have a high mortality, the level of systolic blood pressure before infusion is more closely associated with outcome.[9]

Anisoylated plasminogen streptokinase activator complex (APSAC)

This *second generation* thrombolytic agent consists of streptokinase bound to lys-plasminogen to form an activator complex, and therefore a direct plasminogen activator.[1] The anisoylation protects the molecule from plasmin inhibitors; once in circulation, the agent becomes active following deacylation. The drug was shown to be able to bind to endothelial cells in culture, to human fibrin and plasma clots,[11,12] and this may explain its long half-life (Table 1), which allows it to be administered as a single bolus over 5 minutes. Although there is evidence of fibrin specificity *in vitro*, there is no evidence of this *in vivo* because administration of APSAC induces systemic activation of fibrinolysis (decrease in plasma levels of fibrinogen and other coagulation factors, increase in plasma levels of FDP). Furthermore, the drug possesses the same antigenicity characteristics and produces the same effects on blood pressure as streptokinase.

Urokinase

Urokinase is a 2-chain serine protease which activates plasminogen directly without forming an activator complex and, like streptokinase, is not specific for fibrin-bound clot.[1]

First isolated from human urine, urokinase has generally been synthesized from human fetal kidney tissue culture; therefore it is non antigenic and lacks the problems of neutralization by antibodies. Hypotension is not routinely encountered.

This drug has been administered recently in association with t-PA, in the hope of taking advantage of the systemic effects of the former and the rapid thrombolytic activity of the latter.[13,14] The results indicate the important role of fibrinogen and FDP levels in the occurrence of reocclusion. This further stresses the importance of considering all the various effects of

Table 1. Characteristics of the main thrombolytic agents.

	SK	APSAC	UK	t-PA	pro-UK
Molecular weight (kD)	47	131	35-55	63-70	47
Fibrin specificity	No	No	No	Yes	Yes
Metabolism	Hepatic	Hepatic	Hepatic	Hepatic	
Half-life (min)	18-23	70-120	14-20	3-4	6-8
Antigenicity	Yes	Yes	No	No	No

SK: streptokinase; APSAC: anisoylated plasminogen streptokinase activator complex; UK: urokinase; t-PA: tissue plasminogen activator; pro-UK: prourokinase

thrombolytics on the hemostatic system and not only their ability to lyse the clot.

Fibrin-specific drugs

Tissue plasminogen activator

Native tissue plasminogen activator (t-PA) is a serine protease consisting of a single-chain glycoprotein with a molecular weight of 70 kD;[1] amino acids account for 84% of the molecule, and carbohydrates for the remaining 16%. For thrombolytic therapy recombinant t-PA is employed. The main characteristic of this drug is its fibrin specificity, since the presence of fibrin greatly increases its ability to convert plasminogen into plasmin. *In vivo* administration of t-PA is, however, associated with a slight decrease in fibrinogen levels,[15,16] but systemic activation of fibrinolysis is much lower than that observed after streptokinase administration. It has been suggested that weight-adjusted dosing is essential to providing an optimal risk-benefit ratio for the use of t-PA during myocardial infarction;[17,18] thus, most studies support weight-adjusted, rapid (90 minutes) infusion.[1] Another important factor influencing the efficacy of this agent is cardiac output. In fact, in a recent study cardiac output was found to be significantly higher in the group of patients not responsive to thrombolytic therapy.[19] These data suggest that cardiac output and consequently liver blood flow might lead to variations in t-PA plasma levels and might determine the success or failure of therapy; the very short half-life of the drug (Table 1) is probably important in this context, because it could help to amplify the effects of greater or less hepatic breakdown in different patients. These results could explain a tendency toward reocclusion in patients with improvement of cardiac function upon reperfusion, and a bleeding tendency in patients with depressed cardiac function.

Compared with streptokinase, t-PA shows more rapid thrombolytic activity; its administration is followed by a higher patency rate of the occluded coronary artery, but it is also associated with a significantly higher percentage of reocclusions.[1] The final results of streptokinase and t-PA in terms of survival are very similar, as is demonstrated by two large controlled clinical trials: the GISSI-2 and the ISIS-3.[20]

Prourokinase

Prourokinase is a short-lived, single-chain precursor of urokinase that exhibits relative fibrin specificity, perhaps because a component in plasma competes with plasminogen for binding of this factor, a process which is inhibited by fibrin.[1]

The thrombolytic activity of prourokinase is similar to that of t-PA. In a recent study prourokinase was shown to require heparin for optimal clot lysis in a canine femoral artery thrombosis model.[21] In another study, in man, the effects of prourokinase were compared with those of streptokinase in acute myocardial infarction: the reperfusion rate was higher with prourokinase after 60 minutes and similar with both agents after 90 minutes.[22] In this last study prourokinase was shown to induce lower systemic activation of fibrinolysis than that observed with streptokinase.

Antithrombotic effects of fibrinolytic drugs

As outlined above, fibrinolytic drugs exert different effects on the hemostatic balance. The final result is obviously antithrombotic, but it is important to consider all the different actions of thrombolytics on hemostasis, because this may help to explain and possibly to prevent therapeutic failures or reocclusions.[23] The antithrombotic effects of fibrinolytic drugs are summarized in Table 2.

Recanalization of the occluded coronary artery

Reperfusion in the occluded coronary artery is the main goal of thrombolytic therapy, and all the drugs described above are able to achieve it in a percentage of cases significantly higher than achieved in controls. The early patency rate (60-90 minutes) after administration of fibrin-specific drugs is higher than that observed with streptokinase, APSAC or urokinase; however, patency rates after 2-3 hours are very similar for both groups of thrombolytics, and they remain so after 24 hours and in subsequent days.[1]

The importance of early patency of the

Table 2. Antithrombotic effects of fibrinolytic drugs

- Recanalization of the occluded coronary artery
- Anticoagulant activity (decrease in plasma levels of fibrinogen, factor V and factor VIII; increase in plasma levels of FDP)
- Decreased blood viscosity

infarct-related artery has been confirmed in recent studies, which have demonstrated its beneficial effects on left ventricular function.[24-26] In other investigations several primary and ancillary markers of reperfusion were validated with coronary angiography, and it was found that a rapid and progressive decrease in pain and ST elevation is a reliable marker of reperfusion.[27,28]

Establishment of patency is the primary beneficial effect from thrombolytic therapy, and this explains continuing efforts to increase reperfusion and decrease reocclusion rates.[29-31]

Anticoagulant activity

As described above, all thrombolytic agents are able to induce a decrease in plasma levels of fibrinogen, factor V and factor VIII and an increase in plasma levels of FDP. The effect is best observed with non fibrin specific drugs, but it is also present with the others.[15,32]

The anticoagulant activity of fibrinolytic drugs plays a very important role in the final effect of thrombolysis. In the acute phase of a thrombotic disease the forming clot undergoes dynamic remodeling, with spontaneous lysis on one hand, but also with new fibrin deposition on the other. Therefore it is essential to increase lysis and at the same time inhibit fibrin generation, since clot lysis alone is ineffective if thrombus accretion is not stopped. This hypothesis has been confirmed in clinical studies showing that low plasma levels of fibrinogen and high plasma levels of FDP were associated with higher reperfusion and lower reocclusion rates in patients with myocardial infarction treated with thrombolytics alone or in combination.[14,22]

The higher anticoagulant effect of non fibrin-specific drugs may explain why the results in terms of survival are very similar for both groups of thrombolytics, although fibrin-specific ones show more rapid fibrinolytic activity.

Decreased blood viscosity

Another important aspect of the antithrombotic effect of thrombolytics is their ability to decrease blood viscosity, which may significantly influence blood flow and therefore perfusion of the ischemic tissue. It is known that plasma viscosity depends mainly on fibrinogen levels, while blood viscosity depends in part on the former, but above all on hematocrit and on red cell aggregability.

In the acute phase of myocardial infarction blood viscosity increases as a result of increased hematocrit and plasma fibrinogen levels.[33]

In patients given thrombolytics plasma viscosity decreases, and the effect is more evident with non fibrin-specific drugs, which produce a more marked decrease in fibrinogen levels.[34] Blood viscosity is also reduced by the treatment, in part because of the decrease in fibrinogen levels and, more importantly, because of the decrease in hematocrit due to hemodilution, which may be explained by fluid balance, infusion policy and the use of contrast agents for coronary angiography.[33] Therefore several factors may influence this important parameter in the acute phase of myocardial infarction, and thrombolytic drugs that cause extensive fibrinogen breakdown could offer a more significant benefit than others. No controlled trial, however, has been undertaken to elucidate the precise influence of viscosity on reperfusion, reocclusion and survival.

Prothrombotic effects of fibrinolytic drugs

The possible prothrombotic effects of thrombolytics are listed in Table 3.

Exposure of atherosclerotic plaque under the thrombus

The thrombus occluding a coronary artery, which is responsible for acute myocardial infarction, almost always forms on a fissured atherosclerotic plaque. It is obvious that clot lysis results in re-exposure of the plaque to platelets and coagulation factors, and immedi-

ate reocclusion may follow. Paradoxically, the quicker and more complete the lysis, the higher the risk of a new thrombosis. Reocclusion, however, is not the rule, probably for various reasons, including the anticoagulant effect of thrombolytics, the concomitant administration of antiplatelet and/or anticoagulant drugs and even incomplete lysis of the occluding thrombus.

In any case, it is important to recognize that thrombolytic treatment is associated by definition with a significant risk of reocclusion, and that simultaneous administration of other drugs effective on the hemostatic system is advisable, particularly when fibrin-specific thrombolytic agents are employed.[30,35] Antiplatelet therapy should be continued after the acute event, since an increase in platelet function is often encountered in post-infarction patients,[36] and such treatment offers worthwhile protection against a new infarction, stroke, and death.[37]

Activation of platelet function

As outlined above, clot lysis results in exposure of an atherosclerotic plaque, which in turn may stimulate platelet adhesion and aggregation.[38]

Other possible mechanisms of platelet activation during thrombolytic therapy in acute myocardial infarction include plasmin generation,[1,10] high plasma levels of antibodies to streptokinase,[39] and exposure of fibrin-bound thrombin.[40] Whatever the mechanism(s), the ability of thrombolytics to activate platelet function is well documented.[41-43] Experimental and clinical evidence suggests that such activation plays an important role in the final effect of the treatment. In a canine model of coronary thrombosis, it was found that inhibition of thrombin in addition to treatment with t-PA resulted in enhanced thrombolysis; a combination of inhibition of thrombin and thromboxane synthetase and blockade of thromboxane A_2 receptor further increased reperfusion and decreased reocclusion rates;[44,45] similar results were obtained in the rabbit.[46] In man antiplatelet drugs were also shown to increase the efficacy of thrombolytics in patients with myocardial infarction.[30,47,48,49]

Table 3. Prothrombotic effects of fibrinolytic drugs.

- Exposure of atherosclerotic plaque under the thrombus
- Activation of platelet function
- Activation of coagulation cascade
- Diffuse atheromasic embolization

Activation of the coagulation cascade

Activation of the coagulation process occurs in the acute phase of myocardial infarction;[50] exposure of an atherosclerotic plaque and of fibrin-bound thrombin by thrombolytics may increase such activation, as is demonstrated by high plasma levels of fibrinopeptide A observed in patients with myocardial infarction given thrombolytics, and by the decrease of such levels after administration of heparin.[29]

In vivo thrombin generation in these patients is also suggested by increases in plasma concentrations of prothrombin fragment 1.2 and thrombin-antithrombin III complexes.[51,52]

Therefore, thrombolytics are often administered in association with heparin, usually with good results,[53] but experimental evidence suggests that hirudin could be more effective, probably because it is able to also inhibit fibrin-bound thrombin.[40,54] This hypothesis, however, needs to be tested in controlled clinical trials.

Diffuse atheromasic embolization

This is a rare but very severe complication of thrombolytic treatment, observed so far only with non fibrin-specific drugs.[55] This syndrome is caused by multiple cholesterolic embolism: fragments of atheromatous plaques, probably disrupted by thrombolytics, may embolize and occlude arterial vessels in different organs. Diffuse atheromasic embolization may be suspected in patients with severe and disseminated atherosclerotic lesions who show clinical evidence of acute arterial occlusion after thrombolytic therapy.

This complication, although very severe, should not counterindicate fibrinolytic drugs, since it is very rare and totally unpredictable.

New perspectives in thrombolytic therapy

Accelerated infusion of thrombolytic drugs

A clinical trial named GUSTO (*Global Utilization of Streptokinase and t-PA for Occluded Coronary Artery*) was designed to compare new, aggressive thrombolytic strategies with standard thrombolytic regimens in acute myocardial infarction.[56]

Thirty-day mortality was significantly lower in the group receiving accelerated t-PA infusion and intravenous heparin than in those receiving streptokinase and subcutaneous heparin, streptokinase and intravenous heparin, or a combination of streptokinase plus t-PA with intravenous heparin.

The mechanism of the favorable effect of accelerated t-PA infusion seems to be a more rapid and complete restoration of coronary flow through the infarct-related artery.[57] Further analysis of data from GUSTO and other trials will clarify whether the accelerated t-PA strategy can confidently be recommended for general use.

New thrombolytic agents

Studies are in progress to synthesize or to test new, more powerful agents, including variants and hybrids of t-PA and prourokinase, staphylokinase and plasminogen activator from bat saliva.[30] At present it is impossible to predict whether or not such new possibilities will offer real advantages.

Thrombus-targeted thrombolytic drugs

Although no difference exists in terms of survival between fibrin-specific and non fibrin-specific thrombolytic agents, the idea of lysing only fibrin in the thrombus remains attractive, and new strategies have been considered or partially tested in this contest: e.g. the use of thrombolytics conjugated with fibrin-specific monoclonal antibodies, the use of bifunctional antibodies that contain a fibrin-specific monoclonal antibody and a t-PA-specific monoclonal antibody, the use of thrombolytics conjugated with monoclonal antibodies that recognize epitopes on the surface of activated platelets, such as glycoprotein IIb/IIIa or thrombospondin.[30,31]

Association with other drugs effective on hemostatic system

Although a powerful anticoagulant, heparin is not the ideal protection against thrombus accretion, mainly because it does not inhibit fibrin-bound thrombin and its activity depends strictly on antithrombin III.[58] Other more attractive anticoagulant agents, potentially able to resolve these problems, are under investigation; they include hirudin, hirudin analogues and synthetic thrombin inhibitors, like argatroban or *D-phenylalanyl-propyl-arginyl-chloromethyl ketone* (P-PACK).[30] Alternatively, inhibition of coagulation could be achieved with activated protein C, which was shown to possess antithrombotic properties in a primate model of arterial thrombosis.[59] Inhibition of platelet function is also important during thrombolytic treatment, and new strategies are being considered in this area: monoclonal antibodies directed against glycoprotein receptor IIb/IIIa and disintegrins, which are able to bind integrins and control platelet activation.[30]

Association with other drugs not effective on hemostatic system

In spite of the great effort to increase the clinical efficacy of thrombolytics with new strategies, it is possible that further progress may someday result from an association with other drugs not effective on hemostasis but potentially important in myocardial infarction, like β-blocking agents, ACE-inhibitors and nitrates.[60,61] Controlled trials are in progress to elucidate these points.

Conclusions

In conclusion, many problems have been solved but several points remain obscure in the fascinating problem of lysing a coronary thrombus responsible for myocardial infarction. Some goals are obvious and certainly effective, although often difficult: reduction of delays between onset of symptoms and delivery of thrombolytics,[62] careful evaluation of inclusion and exclusion criteria,[63] particular attention to minimizing the risk of administering thrombolytic therapy inappropriately.[64] In fact, wide

variability still exists in the clinical results of such therapy in different countries.[65]

More in general, it is difficult at present to predict whether or not the new antithrombotic strategies will produce further advantages in terms of reperfusion, reocclusion and survival. Thrombolytics possess both antithrombotic and prothrombotic effects and it is possible that better results may be obtained with new concomitant antiplatelet and/or anticoagulant treatments, but it could be difficult to standardize such powerful and specific treatments for the whole population of patients, and the side effects might increase significantly. When the results of the controlled trials currently in progress are available, it will be possible to answer some of these still open questions.

In any case, thrombolytics are already the treatment of choice for acute myocardial infarction and the first priority must be a continuing effort to increase the percentage of patients treated with these drugs.

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