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Review Article

The ideal fibrinolytic: can drug design improve clinical results?

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Introduction

Thrombolytic therapy has been a major milestone in the management of acute myocardial infarction. By restoring patency in the infarct-related vessel, early administration of thrombolytic therapy reduces the extent of myocardial damage, lowers the risk of morbidity, and prolongs survival. Importantly, however, the available thrombolytic agents have several limitations that may result in less than optimal outcomes. For instance, depending on the agent, only 30% to 60% of patients achieve TIMI (Thrombolysis in Myocardial Infarction) grade 3 flow at 90 min with the current regimens[1,2]. The 30-day mortality rate has averaged 6 to 8% in clinical trials and is likely to be much higher in the practice setting[3–6]. The rate of reinfarction stands at 4%[3–6]. The risk of bleeding remains a concern as well, with the rate of intracranial haemorrhage averaging 0·5% to 0·9% and the rate of transfusion more than 2%[3–6]. Another key issue is the need for more convenient administration. Because of their rapid clearance, both tissue type plasminogen activator and streptokinase must be administered by continuous intravenous infusion.

To try to overcome these drawbacks, several newer thrombolytic therapies have been developed. The development of the second-generation agent, reteplase, was a first attempt. Clinical trials of equivalence have demonstrated that reteplase is at least as effective as streptokinase[6], but have failed to demonstrate superiority over the current gold standard therapy, accelerated tissue type plasminogen activator[4]. Although reteplase can be given in two intravenous bolus doses, they must be administered precisely 30 min apart, somewhat mitigating convenience of administration.

Key Words: Fibrinolytics, acute myocardial infarction, thrombolytic therapy.

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Several additional agents are in advanced stages of clinical development, including mutants of tissue type plasminogen activator (tenecteplase, lanoteplase), staphylokinase, saruplase (pro-urokinase), and vampire bat plasminogen activator. Targets for modification have included half-life, fibrin specificity, resistance to plasminogen activator inhibitor-1, and antigenicity. Alterations in these factors could confer substantial clinical benefits.

Desirable features of the ideal thrombolytic

The characteristics of an ideal thrombolytic agent are summarized in Table 1. Such a drug would provide rapid reperfusion, would establish TIMI grade 3 flow in nearly all patients, and would have a prolonged half-life that permits single-bolus dosing, facilitating more timely and convenient administration. The agent would also have enhanced fibrin specificity to allow preferential activation of fibrin-bound plasminogen at the clot surface, resulting in increased potency and speed to patency. Furthermore, higher fibrin specificity would limit activation of circulating plasminogen and thus degradation of fibrinogen — attributes that would be expected to reduce the risk of bleeding.

Table 1 Characteristics of the ideal thrombolytic agent

- Rapid reperfusion
- 100% TIMI grade 3 flow reperfusion
- Administration as an intravenous bolus
- Fibrin specific
- Low incidence of systemic bleeding
- Low incidence of intracranial haemorrhage
- Resistant to plasminogen activator inhibitor-1 (PAI-1)
- Low reocclusion rate
- No effect on blood pressure
- No antigenicity
- Reasonable cost

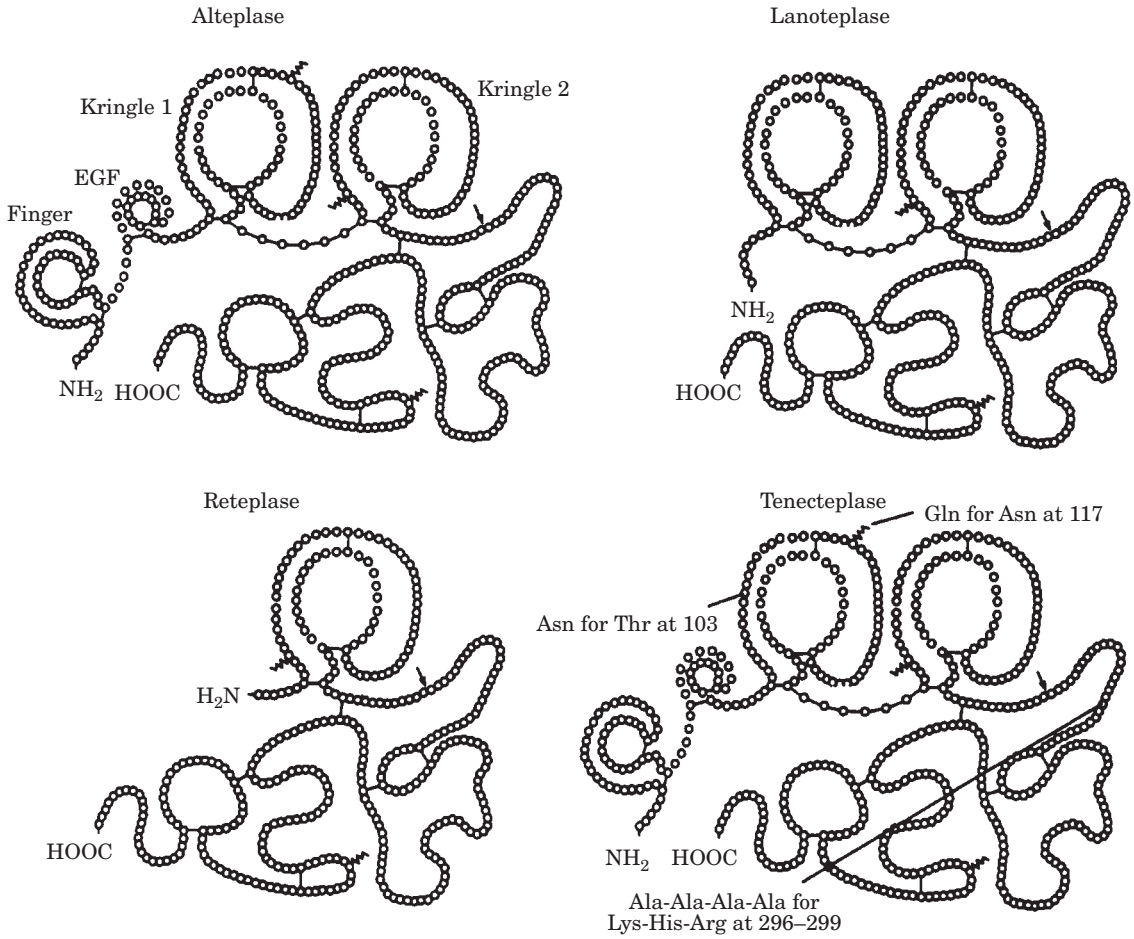

Figure 1 **Molecular structures of tissue type plasminogen activator and newer thrombolytic agents (Reprinted with permission from Brener SJ and Topol EJ. Third-generation Thrombolytic Agents for Acute Myocardial Infarction. In: Topol E, ed. Acute Coronary Syndromes. Marcel Dekker Inc., New York).**

Because plasminogen activators can be inhibited by plasminogen activator inhibitor-1, greater resistance to this inhibitor would further promote potency. The ideal agent would be associated with a low reocclusion rate. Like tissue type plasminogen activator, it would have no deleterious effect on blood pressure, such as that seen with streptokinase. In addition, the ideal thrombolytic would be non-antigenic (permitting repeat administration, if necessary), and would be available at a reasonable cost. The ideal agent should also be less procoagulant, a paradoxical effect of several current thrombolytics. Although it may not be possible to fulfil all these criteria, strides are being made toward the achievement of these goals.

Recently, increased attention has also focused on the prospect of using thrombolytic agents in combination with more potent antiplatelet/antithrombin therapies, such as glycoprotein IIb/IIIa receptor antagonists, direct thrombin inhibitors, and low-molecular-weight heparin. These adjunctive treatments hold promise not only for improving the rapidity of reperfusion and increasing patency rates, but also for reducing the risk of reocclusion.

Newer thrombolytic agents

The molecular structures of the new thrombolytic agents are displayed in Fig. 1. Some of these drugs have been bioengineeered to have specific pharmacological characteristics, whereas others are simply mutations and variants of existing therapies. The key characteristics of these drugs are summarized in Table 2.

Tenecteplase

Tenecteplase is a multiple-point mutation of tissue type plasminogen activator, rather than a deletion mutant (as in the case of reteplase). Tenecteplase has been specifically bioengineered to have an extended half-life, allowing convenient single-bolus dosing, while also maintaining a high level of fibrin specificity and potency[7,8]. In addition, tenecteplase is non-antigenic.

Tenecteplase is unique among variants of tissue type plasminogen activator in that its potentially beneficial modifications (prolonged half-life, higher

Table 2 Key characteristics of newer fibrinolytic agents compared with t-PA

Characteristic	t-PA	TNK-t-PA	Lanoteplase	Staphylokinase	Saruplase	Vampire bat PA
Molecular weight	70 000 D	70 000 D	53 500 D	16 500 D	46 500 D	52 000 D
Immunogenicity	No	No	?	Yes	No	Yes
Plasminogen activation	Direct	Direct	Direct	Indirect	Direct	Direct
Fibrin specificity	++	+++	+	+++(+)	+	+++(+)
Plasma half-life	4–8 min	20 min	37 min	6 min	9 min	2·8 h
Dose	15 mg bolus plus 3 h infusion up to 85 mg	$\pm$ 0·5 mg . kg^{-1} single bolus	120 KU . kg^{-1} single bolus	15 mg+15 mg double bolus or 30 mg over 30 min	20 mg bolus +60 mg infusion over 1 h	?
PAI-1 resistance	No	Yes*	?	?	?	?

t-PA=tissue type plasminogen activator; TNK-t-PA=tenecteplase; PAI-1=plasminogen activator inhibitor-1.
*Only tenecteplase has been specifically bioengineered and assessed for plasminogen activator inhibitor-1 resistance.

fibrin specificity, and resistance to plasminogen activator inhibitor-1) have been achieved at no cost in terms of fibrin binding or biological activity against fibrin-rich clots[7,8]. Tenecteplase has a more than 14-fold greater fibrin specificity and an 80 times greater resistance to inactivation by plasminogen activator inhibitor-1 than does tissue type plasminogen activator, resulting in a greater affinity of tenecteplase for fibrin-rich clot[8].

DeMarco *et al.* demonstrated that tenecteplase does not produce the paradoxical procoagulant effects that limit other thrombolytic agents. Two hours after administration of tenecteplase, thrombin–antithrombin complex, a marker of thrombin generation, was comparable to control values[9]. Tenecteplase's enhanced fibrin specificity may also increase the speed to patency and permit compatibility with new adjunctive therapies. Furthermore, tenecteplase is 10-fold more effective at conserving plasma fibrinogen than tissue type plasminogen activator and does not induce a significant depletion of α_2-antiplasmin, indicating less of a systemic fibrinolytic effect.

In animal models of acute arterial occlusion, bolus administration of tenecteplase has been associated with a 6- to 12-fold greater thrombolytic potency (extent of clot lysis) than accelerated tissue type plasminogen activator on a $\mu g \cdot kg^{-1}$ basis[8–11]. This has been attributed to tenecteplase's significantly slower plasma clearance, which results in increased exposure of clot to the agent and more than compensates for a slightly lower level of plasma clot lysis activity. Pre-clinical testing has also revealed faster reperfusion, faster clot lysis, longer duration of arterial patency, and lower occurrence of bleeding compared with tissue type plasminogen activator[9–11].

The pharmacokinetics of tenecteplase have been further elucidated in clinical studies. An analysis from the phase I TIMI 10A trial evaluated data from 82 patients with myocardial infarction who received single-bolus doses of tenecteplase ranging from 5 to 50 mg. The time courses of the mean immunoreactive tenecteplase plasma concentrations for these doses were compared with the plasma concentration curve for 100 mg tissue type plasminogen activator (using the accelerated 90 min dosing regimen)[12]. The estimated peak tenecteplase plasma concentrations increased in a dose-dependent fashion. After administration of the bolus injection, the elimination of tenecteplase from plasma exhibited a biphasic pattern: the initial phase had a mean half-life ranging from 11 ± 5 to 20 ± 6 min and was followed by a slower terminal phase with a mean half-life ranging from 41 ± 16 to 138 ± 84 min. Across all doses, the mean clearance of tenecteplase from plasma was 151 ml . min^{-1} (with a range of 216 ± 98 ml . min^{-1} at the 5 mg dose to 125 ± 25 ml . min^{-1} at the 50 mg dose). The mean residence time in the body was approximately 1 h. Compared with the data reported for tissue type plasminogen activator, the plasma clearance of tenecteplase was approximately two- to fourfold slower.

The pharmacokinetic characteristics of tenecteplase suggest that this agent may offer important clinical advantages — a prospect that has been confirmed in initial clinical trials of patients with acute myocardial infarction. In the TIMI-10A trial, which included a total of 113 patients, the efficacy and safety profiles of tenecteplase were encouraging[13]. At 90 min, TIMI grade 3 flow was achieved in 59% and 64% of patients treated with the 30 and 50 mg doses, respectively. Systemic fibrinogen and plasminogen levels decreased by only 3% and 13%, respectively, at 1 h after tenecteplase administration, indicating minimal activation of the fibrinolytic system. Seven patients (6·2%) had a major haemorrhage, six at the vascular access site and one after bypass surgery. No strokes or intracranial haemorrhages occurred. The sample size was too small for statistical significance, but the following end-points are interesting as reference points: mortality was 3·5% at 30 days and the reinfarction rate 4·4%. No antibodies to tenecteplase were evident in any patient at 30 days.

The phase II TIMI-10B trial randomized 886 patients to receive 30 or 50 mg of tenecteplase or accelerated tissue type plasminogen activator 100 mg[14]. The 50 mg tenecteplase dose was replaced early in the study by a 40 mg dose because of increased bleeding, and heparin doses were reduced, as discussed in more detail below. Identical rates of TIMI grade 3 flow were achieved at 90 min with the 40 mg single-bolus dose of tenecteplase and accelerated tissue type plasminogen activator (63%). A trend toward a higher rate of TIMI grade 3 flow was

evident at 60 min with the 40 mg dose of tenecteplase as opposed to tissue type plasminogen activator (55% vs 48%, respectively). Reperfusion was also evaluated on the basis of corrected TIMI frame counts. An analysis of patent vessels showed a trend toward more rapid reperfusion with the 40 mg dose of tenecteplase than with accelerated tissue type plasminogen activator[15]. A simple, four-step weight-based dosing schedule (0·5 to 0·55 mg . kg^{-1}) is required to achieve maximal reperfusion.

Analyses of data from the initial cohorts enrolled in the TIMI-10B trial showed that activated partial thromboplastin time levels were high in some patients who experienced intracranial haemorrhage[16]. The protocol was subsequently revised to lower heparin doses in lightweight patients. A 5000 U heparin bolus and an initial 1000 U . h^{-1} infusion was administered to patients who weighed >67 kg, and a 4000 U bolus plus 800 U . h^{-1} infusion was administered to those who weighed <67 kg. After reduction of the heparin doses, the rate of intracranial haemorrhage in all patients decreased significantly, and patency rates at 90 min were comparable to those in the initial cohorts. In ASSENT-1, the rate of intracranial haemorrhage was 0·62% in patients receiving a reduced heparin dose and the 40 mg dose of tenecteplase[16]. Some investigators have suggested that the enhanced potency, higher plasminogen activator inhibitor-1 resistance, and slower clearance of tenecteplase may even obviate the need for heparin[17]. This possibility is supported by data from an animal model of arterial occlusion, which showed that administration of a single bolus of tenecteplase without heparin maintained thrombolytic efficacy while eliminating the occurrence of bleeding. Other studies have shown that tenecteplase has a less procoagulant effect than other thrombolytics[9].

TIMI grade 3 flow in these phase II trials was analysed by dose:weight ratio. A weight-adjusted dose of 0·50 to 0·55 mg . kg^{-1} was found to provide optimal reperfusion, and was therefore selected for use in further clinical testing.

The phase III ASSENT-2 trial, which has enrolled 16 949 patients, compared single-bolus tenecteplase with accelerated tissue type plasminogen activator, aiming to show clinical equivalence of both agents in terms of 30 day mortality. Preliminary results of this trial were presented at the American College of Cardiology Scientific Sessions in March 1999. Identical mortality rates at 30 days were observed with the two agents: 6·2%. Intracranial haemorrhage rates were also very similar with a trend towards fewer cerebral bleedings in older patients and women with tenecteplase. Significantly fewer non-cerebral bleedings were also noted with tenecteplase.

Lanoteplase

Lanoteplase is a deletion and point mutant of wild-type tissue type plasminogen activator, in which the finger and epidermal growth factor domains have been removed and the glycosylation points in kringle 1 have been modified[18]. While no data have been reported, its developers describe lanoteplase as fibrin-selective[19]. Furthermore, in a study of 21 patients with acute myocardial infarction a smaller increase in plasminogen activator inhibitor-1 plasma levels was observed after lanoteplase than after tissue type plasminogen activator, which might result in a lower reocclusion rate[20]. The plasma half-life of lanoteplase is 37 min, indicating that it is appropriate for administration as a single bolus.

Lanoteplase was evaluated in a randomized, double-blind, phase II trial, Intravenous nPA for Treatment of Infarcting Myocardium Early (InTIME)[21]. A total of 602 patients with suspected myocardial infarction received a standard 90 min infusion of tissue type plasminogen activator or a single bolus dose of lanoteplase — 15, 30, 60, or 120 kU . kg^{-1} — within 6 h of symptom onset. Lanoteplase was found to have a dose-dependent effect on reperfusion rates. Although the trial was not designed to assess efficacy, the highest lanoteplase dose (120 kU . kg^{-1}) was significantly more effective than tissue type plasminogen activator with regard to the rate of TIMI grade 2/3 flow at 90 min (83% vs 71%, respectively; $P<0·05$). Analysis of TIMI grade 3 flow rates at 90 min showed a non-significant trend favouring the highest lanoteplase dose (57% vs 46% with tissue type plasminogen activator; $P=0·11$). The two drugs had similar safety profiles, with moderate or major bleeding complications occurring in 8·1% and 10·5% of the high-dose lanoteplase and tissue type plasminogen activator groups, respectively. One haemorrhagic stroke occurred in the tissue type plasminogen activator group and none in the lanoteplase group. At 30 days, the incidence of the composite end-point of death, heart failure, non-fatal reinfarction, or major bleeding did not differ significantly between the two treatment groups, although the trend favoured lanoteplase over tissue type plasminogen activator (11% vs 24%, respectively).

A phase III mortality trial, called InTIME-II, comparing single-bolus lanoteplase and accelerated tissue type plasminogen activator in 15 078 patients, has been completed. The results were also presented at the American College of Cardiology meeting in March 1999. Similar 30 days mortality rates were found: 6·8% for lanoteplase and 6·6% for tissue type plasminogen activator. However, significantly more cerebral bleedings occurred in the lanoteplase group:1·13% vs 0·62% in the tissue type plasminogen activator group ($P=0·003$).

Staphylokinase

Staphylokinase is a protein produced by certain strains of *Staphylococcus aureus*. Like streptokinase, staphylokinase forms a 1:1 stoichiometric complex with plasminogen. However, unlike the streptokinase–plasminogen complex, the staphylokinase–plasminogen complex must be converted to a staphylokinase–plasmin complex before it can become active. Also in contrast to the streptokinase–plasminogen complex, the

staphylokinase–plasmin complex is rapidly neutralized by α_2-antiplasmin in plasma in the absence of fibrin. In the presence of fibrin, the rate of inhibition by α_2-antiplasmin is reduced by more than 100-fold, resulting in a high degree of fibrin selectivity[22]. The initial plasma half-life of staphylokinase (6·3 min in phase I trials[23]) does not support single-bolus administration.

To date, the clinical experience with staphylokinase in the treatment of acute myocardial infarction has been encouraging, but is limited. The STAR trial, a multicentre investigation designed to assess plasma fibrinogen levels and coronary artery patency, randomized 100 patients to receive either of two staphylokinase doses (10 or 20 mg) or accelerated tissue type plasminogen activator[24]. The staphylokinase groups received 10% of the dose in an initial bolus, with the remainder of the dose administered in a 30 min infusion. Systemic fibrinogen degradation, α_2-antiplasmin consumption, and plasminogen activation were substantial with tissue type plasminogen activator, but absent with staphylokinase. These observations confirmed that staphylokinase is highly fibrin-specific. At 90 min, the rate of TIMI grade 2/3 flow was 71% with staphylokinase 10 mg and 83% with 20 mg, as compared to 83% with tissue type plasminogen activator. TIMI grade 3 flow was achieved in 50%, 74% and 62% of patients, respectively. The differences between groups were not statistically significant. The incidence of bleeding was slightly lower with staphylokinase than with tissue type plasminogen activator (21% vs 31%, respectively), but this difference was not significant. A non-significant trend toward a lower rate of in-hospital mortality was observed with staphylokinase vs tissue type plasminogen activator; however, the investigators cautioned that this finding may have been coincidental because the tissue type plasminogen activator group inadvertently contained a larger number of sicker patients (more previous myocardial infarction and Killip class >1).

In the wake of a pilot study demonstrating the feasibility and safety of a double-bolus administration of staphylokinase[25] a multicentre, randomized trial was undertaken to compare this approach with accelerated tissue type plasminogen activator in 102 patients[26]. The staphylokinase group received two bolus doses of 15 mg each, given 30 min apart. At 90 min, TIMI grade 2/3 flow was observed in 84% of patients in each group. TIMI grade 3 flow was achieved in 68% of the staphylokinase group and 57% of the tissue type plasminogen activator group; this difference was not statistically significant. Data from this study also suggested that, because of its higher degree of fibrin specificity, staphylokinase may have less potential for procoagulant effects when compared with tissue type plasminogen activator[27].

Of continuing concern, however, is the fact that staphylokinase has considerable antigenicity, as reflected in data from the STAR trial[24], the double-bolus trial[26], and earlier clinical investigations[28]. Within 2 weeks of treatment, the vast majority of patients develop neutralizing antibodies to staphylokinase that remain elevated for several months[24,26,28]. These findings imply that patients treated with staphylokinase would be refractory to repeat administration of the drug[29]. Researchers are currently exploring the possibility of developing non-immunogenic variants of staphylokinase.

The CAPTORS trial of staphylokinase is currently under way in Belgium and Canada, performing pharmacokinetic studies with increasing doses of staphylokinase. Phase III trials, which will probably use a pegilated variant with a reduced immunogenicity, have not been designed yet.

Saruplase

Saruplase, a recombinant single-chain glycoprotein produced from genetically transformed *Escherichia coli*, undergoes limited hydrolysis by plasmin in vivo to become two-chain urokinase. The mechanism of action of saruplase is not yet fully understood and the magnitude of its plasmin-generating capability remains a matter of debate[30]. Saruplase is not fibrin-specific. The agent has a half-life of 9 min and is administered as a 20 mg bolus followed by a 60 mg infusion over 1 h. Immunogenciity has not been observed.

In the early phase of development, a randomized, double-blind clinical study in 401 patients found a significantly higher rate of TIMI grade 2/3 flow with saruplase than with streptokinase at 60 min, but comparable rates after 90 min (the primary end-point)[31]. Less fibrinogen consumption and fewer bleeding complications were observed with saruplase, and the risk of intracranial haemorrhage was similar — leading to the hope that this agent might confer both efficacy and safety advantages.

However, the recent COMPASS trial, designed to demonstrate equivalence of saruplase and streptokinase in 3089 patients, found that the rate of intracranial haemorrhage was actually higher with saruplase (0·9%) than with streptokinase (0·3%)[32]. This study found a trend toward a lower incidence of all-cause mortality at 30 days (the primary end-point) with saruplase vs streptokinase (5·7% vs 6·7%, respectively). Overall rates of stroke and reinfarction were likewise similar in the two groups.

The SUTAMI trial found that TIMI grade 2/3 flow rates at 24 to 72 h were comparable with saruplase and urokinase[33]. When compared in the SESAM trial with a 3 h infusion of tissue type plasminogen activator in 473 patients, saruplase was associated with comparably high rates of TIMI grade 2/3 flow at 60 and 90 min[34]. Rates of in-hospital mortality and complications were also similar in the two treatment groups. Single-bolus administration of saruplase has been compared with a 1 h infusion in the BIRD trial. Similar patency rates and clinical outcomes were observed with both dosing regimens[35].

Vampire bat plasminogen activator

The investigational agent vampire bat plasminogen activator, a recombinant form of a protein found in the

saliva of the vampire bat, has been shown to be more fibrin-specific than recombinant tissue type plasminogen activator[36]. The extended half-life of vampire bat plasminogen activator (2·8 h in a phase I clinical study) suggests that this agent would be appropriate for single-bolus dosing[37]. The mean time to reperfusion was comparably fast with vampire bat and tissue type plasminogen activator in an animal model of arterial thrombosis, but vampire bat plasminogen activator was associated with significantly greater maximal blood flow after reperfusion and a markedly delayed median time to reocclusion[38]. Another pre-clinical study found that plasma fibrinogen and factor VIII decreased substantially with tissue type plasminogen activator, but only slightly with vampire bat plasminogen activator, when the two agents were given in doses that yielded similar thrombolytic efficacy[39]. Nonetheless, vampire bat plasminogen activator and tissue type plasminogen activator prolonged bleeding time to a similar extent, and fibrinolytic bleeding episodes actually tended to more protracted with vampire bat plasminogen activator. In addition, animal studies have revealed the potential for immunogenicity after administration of bat-vampire bat plasminogen activator[40]. Although titres are variable, antibodies persist for several weeks. Clinical evaluations of vampire bat plasminogen activator have recently started.

Discussion

Although currently available thrombolytic therapies have greatly improved outcomes in patients with acute myocardial infarction, all these agents are associated with certain limitations. Half or more of the patients will fail to achieve early and complete reperfusion with the current regimens. The rate of mortality at 30 days post-treatment is at least 6 to 8%, and possibly higher. Reinfarction, bleeding risk (including intracranial haemorrhage), and the potential need for transfusion continue to pose concerns.

In a search to overcome these drawbacks, recent research has focused on the development of newer agents with properties that may translate into improved efficacy and safety profiles. Agents currently being developed include tenecteplase, lanoteplase, staphylokinase, saruplase, and vampire bat plasminogen activator. The ideal thrombolytic therapy would offer a variety of advantages over current treatments, including increased potency, a high degree of fibrin specificity, resistance to inactivation by plasminogen activator inhibitor-1, a favourable safety profile, and the convenience of single-bolus administration, with no immunogenicity. Thus far, the available data suggest that tenecteplase may be the best prospect for (partially) fulfilling these criteria. However, considering the patency data and clinical outcomes observed with tenecteplase and the other new agents it is unlikely that any new fibrinolytic agent given together with heparin and aspirin would result in a significantly better outcome when compared with accelerated tissue type plasminogen activator. Nevertheless, if single-bolus administration of a fibrinolytic of equal lytic efficacy and safety as accelerated tissue type plasminogen activator results in an earlier treatment (and therefore in an earlier recanalization of the infarct-related vessel) more patients will be saved.

Another desirable feature is compatibility with newer adjunctive therapies such as the glycoprotein IIb/IIIa inhibitors, which are attracting increasing attention as a means of improving reperfusion, especially at the tissue level. Of interest in this regard are promising findings from the TIMI-14 trial[41]. Data from this trial showed that higher patency rates and more rapid reperfusion were achieved with the combination of a glycoprotein IIb/IIIa inhibitor (abciximab) and 50 mg tissue type plasminogen activator given over 1 h as opposed to abciximab alone, abciximab plus streptokinase, or full-dose accelerated tissue type plasminogen activator alone. These data suggest that even greater efficacy may be achieved if thrombolytic agents with enhanced fibrin specificity are used in combination with powerful antiplatelet therapies. In addition, safety may improve because more fibrin-selective drugs have a lower potential for causing systemic fibrinolysis and bleeding complications. The co-administration of glycoprotein IIb/IIIa inhibitors may also increase the efficacy and safety of angioplasty either performed on a rescue basis in case of failed reperfusion or on an elective basis in the days following the acute event. Ultimately, large-scale clinical trials will be needed to fully ascertain the relative advantages of the newer thrombolytics when given in combination with glycoprotein IIb/IIIa inhibitors.

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