

Opinion

What Fibrinolytic Therapy Can Learn from Endogenous Fibrinolysis; Both Activators Rather Than Only One are Required

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Abstract

Fibrinolytic therapy with Tissue Plasminogen Activator (tPA) alone has been the standard for three decades, but due to its inefficacy and bleeding risk, tPA has been replaced by Primary Percutaneous Coronary Intervention (PPCI) as the treatment of choice for Acute Myocardial Infarction (AMI). By contrast to tPA mono-therapy, natural fibrinolysis uses a sequential combination of both biological activators, tPA and uPA, the native form of which is a proenzyme, prouPA. Both *in vitro* and *in vivo*, tPA and prouPA have complementary modes of action in fibrinolysis and are synergistic when combined. In a published clinical trial, the PATENT study, 101 patients with AMI were treated with a 5 mg tPA bolus (5% of the standard dose) followed by a modest infusion of prouPA. This sequential combination virtually doubled the coronary TIMI-3 infarct artery patency rate and reduced the mortality six-fold compared to the best results with tPA alone.

Introduction

Fibrinolysis is the body's natural defense that prevents physiological fibrin, needed for the repair of wear and tear vascular injuries, from building up and interfering with blood flow. Evidence that this system is ongoing comes from the invariable presence of the fibrinolytic degradation product D-dimer in plasma (110-250 ng/ml). This normal concentration goes up as much as twenty-fold in the presence of thromboembolism, representing endogenous fibrinolysis.

The idea that tPA alone was responsible for this efficient system represents a fundamental misunderstanding of this biological system, which remains to be addressed [1]. Ever since the FDA approved tPA for the treatment of AMI in 1987, it has been the activator choice and it has been used alone. As a result, the current understanding of the clinical benefit of fibrinolysis is based almost exclusively on tPA monotherapy. At the same time, it was well established that there are two plasminogen activators, the second one being Urokinase Plasminogen Activator (uPA), the native form of which is a proenzyme (prouPA) [2]. Both are required for clot lysis *in vitro*, and their fibrinolytic properties are complementary and synergistic in combination. Therefore, the

clinical benefits of the full potential of fibrinolytic therapy remains to be established.

Discussion

With few exceptions, the fibrinolytic clinical experience has been that of tPA or one of its two longer half-life mutant forms. This experience has been sufficiently disappointing that fibrinolysis has become discredited, and it has been replaced by Primary Percutaneous Coronary Intervention (PPCI) as the treatment of choice for AMI. For ischemic stroke, the tPA bleeding risk is higher and has obliged a one third tPA dose reduction which further diminished its efficacy. Even with this reduction, a 6-7% risk of intracranial hemorrhage remains [3]. Due to this risk, reperfusion therapy must be delayed until a careful history and diagnostic studies have eliminated a bleeding risk. Because of these risks tPA treatment of stroke remains "mired in controversy" making a more effective and safer fibrinolytic particularly urgently needed for this indication.

Although PPCI is now the treatment of choice for AMI, it is handicapped by being a hospital procedure that is time-consuming, technically demanding, and costly. This limits the patient

population that can be served, and PPCI is further limited by the time consumed by the procedure. Reduction in AMI mortality is greatest when reperfusion is accomplished within 1-2 hours of the event [4]. When it can be done within 70 minutes, the mortality was 1.2% [5]. Similarly, in animal models the longer the coronary occlusion, the less salvageable myocardium remains [6]. This makes any inpatient treatment particularly challenging. Therefore, it is not only for stroke but also for AMI that a more effective and safer fibrinolytic is needed.

The endogenous fibrinolytic system, in contrast to therapy, uses not one activator but two. Fibrinolysis is initiated by tPA when it is released from the vessel wall at the site of a fibrin clot. The tPA binds to the clot at its fibrin binding site on the D-domain of fibrin and activates plasminogen on the same domain fibrin [7,8]. The unbound tPA is then promptly cleared by its short (5 min) half-life and inhibited by its potent plasma inhibitor (PAI-1). Therefore, tPA does not contribute further to fibrinolysis. The rapid elimination of iv tPA serves the important physiological function of protecting hemostatic fibrin since it has the same tPA binding site as a clot. Lysis of hemostatic fibrin is the main cause of bleeding during tPA therapy [1]. Therefore, the current practice of administering tPA by iv infusion is particularly unphysiological and risky.

After fibrinolysis is initiated by tPA, additional plasminogen binding sites are created which are on the E-domain of fibrin [9] and of which there are two [10]. Plasminogen on the first of these undergoes a conformational change which allows the intrinsic activity of prouPA to activate it [11]. This step is followed by reciprocal activation of prouPA to its enzymatic form (tcuPA) [12] and tcuPA then activates the remaining plasminogen completing fibrinolysis.

This dual activator pathway is consistent with the modes of action of the activators since they are complementary [13] and have a synergistic lytic effect when combined [14]. This mechanism was also corroborated the finding that tPA plasminogen activation was specifically promoted by the fibrin D-domain and that by prouPA is promoted only by the fibrin E-domain [15]. The finding also explains why both tPA and prouPA are required for lysis at fibrin-specific doses. Since uPA activates two fibrin-bound plasminogen, one by prouPA and the other by tcuPA, it is responsible for two-thirds of the fibrinolysis, and tPA one third.

The PATENT trial referred to in the abstract is the only published study in which the endogenous fibrinolytic paradigm of a sequential combination of the activators was tested clinically. In 101 AMI patients a mini bolus (5 mg) of tPA was administered to initiate fibrinolysis. In keeping with the findings that tPA was only responsible for this step, no additional tPA was given and it was followed by a prouPA infusion of 90 minutes. The treatment resulted in a complete infarct artery opening rate of 82% and an AMI mortality of 1% [16]. This result compares with a 45%

opening rate and a mortality of 6.3% in the best of the tPA studies (GUSTO) [17].

Had this fibrinolytic regimen been adopted in 1995 when the PATENT trial was published, almost one million patients who died from AMI in the US since then could have been saved. In Europe, the number of lives that could have been saved would be similar.

Unfortunately, not long after this trial the company that supported the PATENT trial (Farmitalia) was sold to Pharmacia, which abandoned all cardiovascular drug development. Therefore, the opportunity to do a second trial with this combination was lost. More recently, a single site mutant of prouPA has been developed which has the advantage of being five-fold more stable in plasma at therapeutic concentrations, making it much less likely to cause bleeding side effects since these are related to non-specific tcuPA generation. The mutant uPA has all the other properties of native prouPA [18-25] and will be used in a synergistic combination with tPA.

For ischemic stroke, the need for a more effective and safer fibrinolytic is particularly urgent since tPA therapy is both inadequately effective and hazardous. Therefore, a sequential combination of a mini bolus of 5 mg tPA followed by a mutant proUK infusion (40 mg/h), which is safe and highly effective is ideally suited for this condition.

Conclusion

The function of tPA in fibrinolysis is limited to the initiation of fibrin degradation which is accomplished by the fibrin-bound portion of tPA. The traditional administration of tPA by an IV infusion is based on a misunderstanding of how it functions. It is analogous to trying to run a car on only its starting motor. Instead, uPA is responsible for continuing and completing fibrinolysis and the two activators have sequential and complementary modes of action which gives them a synergistic lytic effect when combined. Only by using both activators can all the fibrin-bound plasminogen's be activated at fibrin-specific, safe doses. This concept was validated clinically in a study of AMI. According to the results obtained in this study, had this regimen been adopted in 1995 when it was published, about 50,000 deaths from AMI annually, or close to one million lives, could have been saved. We don't have similar figures for stroke, but it is evident that this regimen of sequential fibrinolysis would have had a major impact on morbidity and mortality in stroke as well.

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Conflicts of Interest

The author is the Scientific Director of TSI, the company developing a uPA mutant for use in therapeutic fibrinolysis.

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