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Mini Review

Why tPA Should Not be Used Alone for Fibrinolytic Therapy

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MONOTHERAPY

Therapeutic fibrinolysis has used tissue plasminogen activator (tPA) alone for thirty-three years, based on the conviction that tPA was responsible for fibrinolysis. However, this assumption should have been put into question from the outset when in the first comparatives clinical trials in acute myocardial infarction (AMI), tPA was compared with streptokinase (SK), a non-specific plasminogen activator with an indirect, inefficient mechanism of action. Therefore, it was expected that the 30-day mortality with tPA treatment would be significantly lower than with SK, which turned out not to be the case.

A total of 95,740 patients had be tested and only in one out of four groups in the last of the three comparative trials was a significant mortality difference found with tPA over SK. Not surprisingly, when these findings were reviewed by a Bayesian analysis, it was concluded that a significant difference between tPA and SK had not been established [1]. Despite these findings, tPA received FDA approval for the treatment of AMI and nine years later it also received approval for the treatment of ischemic stroke. It has remained the fibrinolytic of choice ever since, a triumph of commercial interests over clinical evidence.

tPA is a fibrin-specific fibrinolytic due to its high affinity for blood clot fibrin, which is the property that made it so attractive for fibrinolysis. It binds to one specific site on the D-domain of fibrin close to a plasminogen binding site (Figure 1). As result, a ternary complex is formed between tPA and plasminogen on fibrin and this complex promotes plasminogen activation by tPA about 1,000-fold and initiates fibrinolysis. Therefore, this reaction requires no more than a 5 mg bolus dose of tPA. This results in the activation of one out of the three different fibrin-bound plasminogens whose activation is responsible for fully effective fibrinolysis.

Since tPA has no other fibrin binding site, it cannot activate the other two plasminogens, which are located on the fibrin E-domain (Figure 1). As a result, when tPA is used alone, 100 mg of tPA is required to activate the two other plasminogen. The tPA is infused for 60 minutes, but even at this dose, tPA is a weak plasminogen activator and was never sufficiently effective. This was also evident from the finding that percutaneous coronary intervention (PCI) was more effective than tPA in AMI, despite being significantly slower. This is important since both mortality and tissue damage are inversely related to the time required for reperfusion. PCI is now the treatment of choice in AMI, and procedures like thrombectomy are being increasingly employed for ischemic stroke instead of or in addition to tPA.

This total change in the state of the art from rapid fibrinolysis to time-consuming invasive procedures is a reflection on the inadequacy of tPA.

FIBRINOLYSIS: THE NATURAL DESIGN

The reason for tPA's inadequacy in fibrinolysis is shown by nature's design for fibrinolysis. In contrast to monotherapy, in nature there is a second plasminogen activator in blood called urokinase plasminogen activator (uPA). The native form of

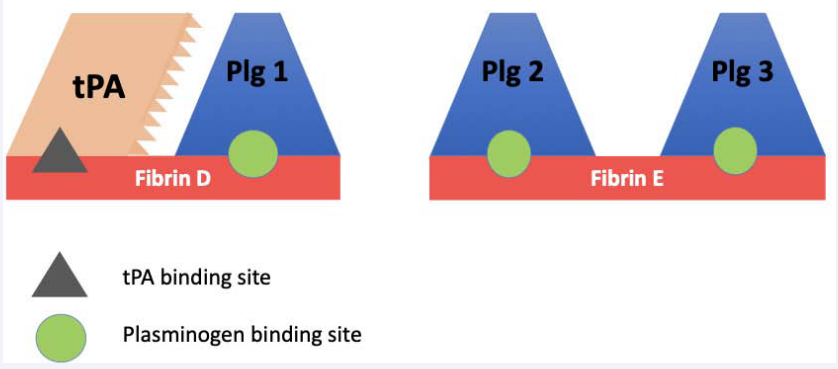

Figure 1 Plasminogen binding site.

uPA is a proenzyme, prouPA, which is stable in plasma and has fibrin-specific fibrinolytic properties [2], though it does not bind to fibrin. In physiological fibrinolysis, tPA initiates fibrinolysis, which is then continued and completed by uPA, prouPA and then two-chain uPA (tcuPA), also called urokinase (UK).

Therefore, tPA and uPA together dissolve the fibrin clot, a mechanism that is both more effective and much safer then when tPA is used alone, since high dose tPA is associated with hemorrhagic complications from tPA binding to and disrupting hemostatic sites.

Since uPA has two active forms, prouPA and tcuPA, whereas tPA has only one, uPA is responsible for 2/3 of fibrinolysis. The combination tPA and uPA is also much safer, since in the combination tPA can be administered by a mini bolus which is sufficient to activate the first plasminogen. Moreover, since tPA and prouPA have complementary modes of action, their combination has a synergistic effect which requires lower, safer doses [3].

Nature's combination regimen was once tested in a clinical study of 101 patients with AMI who were given a 5 mg bolus of tPA followed by a 90-minute infusion of prouPA (40 mg/h) (PATENT study). Compared with the best of the tPA studies (GUSTO), this combination regimen reduced mortality 6-fold (1% vs 6%) and almost doubled the opening of the infarct artery (82% vs 45%) [4]. These findings were consistent with the in vitro clot lysis studies with the combination.

Had the PATENT regimen been adopted at the time it was published, almost one million AMI deaths might have been averted, which in the US alone. Unfortunately, no second study with the regimen was possible since the development of prouPA was discontinued not long after the study.

CONCLUSIONS

It is evident from the above why tPA alone has been an inadequate as well as a risky fibrinolytic. It can activate only one of the three plasminogens responsible for fibrinolysis. In addition, the one plasminogen that tPA activates effectively, is also found on hemostatic sites, which are, therefore, vulnerable to lysis, especially when tPA is given by high dose infusion. This, however, is unnecessary with the combination where only a 5 mg tPA bolus is required, which spares hemostatic sites. As show in the simple diagram below, tPA's fibrin affinity brings it close to only the first plasminogen. The other two are out of reach and are activated by uPA not tPA. Using tPA alone has been a mistake.

All the above information has been in the literature for some years, but like certain other bad habits, the tPA habit remains exceptionally hard to break, as shown by the fact that tPA (and a longer half-life derivative) remain the only plasminogen activators available.

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