



Fibrinolysis Using Monotherapy is Inadequate and Risky

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Abbreviations: UK- Urokinase, proUK- Prourokinase, tPA- Tissue Plasminogen Activator, PAI-1- Plasminogen Activator Inhibitor-1, uPA - Urokinase Plasminogen Activator.

Introduction

Fibrinolysis has been induced by tPA alone for more than 30 years but this has been inadequately effective and associate with bleeding complications including intracranial. As a result, fibrinolysis has been replaced by a catheterization procedure whenever possible, but this is a time-consuming hospital procedure that precludes reperfusion of the occluded artery in time to salvage function. For stroke, tPA remains the only option but is associated with a 6-7% risk of symptomatic intracranial hemorrhage, so that it is used with reluctance.

By contrast to this therapeutic experience, fibrinolysis by the endogenous, physiological system is effective without bleeding side effects. Its efficacy is evidenced by the fibrinolytic product, D-dimer, which is invariably present in blood even in the healthy population, indicating that fibrinolysis is ongoing. The D-dimer normal concentration (112-250 ng) goes up ten-fold or more in the presence of thromboembolism showing that endogenous fibrinolysis has a considerable reserve capacity. This degree of fibrinolytic efficacy is hard to explain as being due to the low endogenous concentration of tPA (10-12 ng/ml) alone. This explanation is made even more unlikely by the presence of Plasminogen Activator Inhibitor-1 (PAI-1) in blood, which is an inhibitor of tPA. Since PAI-1 is one of the most potent biological inhibitors, it suggests that free tPA is considered toxic by the body and indeed a congenital PAI-1 deficiency results in a serious bleeding disorder related to hyper-fibrinolysis [1].

Therefore, unsurprisingly therapeutic infusions of tPA are also associated with hemorrhagic complications. The doses required for efficacy are also high and even then its efficacy is wanting. This is not at all the profile of endogenous fibrinolysis which is both effective and safe. It is evident that the standard state of the art for fibrinolysis and that which is going on in nature are very different.

The Endogenous Fibrinolytic Paradigm

Fibrinolysis according to its natural function requires more than tPA, explaining why it has not been more satisfactory. There is a second plasminogen activator in the biological fibrinolytic system which is both different and complementary to tPA. The second activator is Urokinase Plasminogen Activator (uPA), which has two

fibrinolytically active forms. The native form is a single-chain proenzyme called Prourokinase (proUK) that is activated by plasmin to a two-chain enzyme called Urokinase (UK). ProUK has a fibrin-dependent or fibrin-specific mode of action, whereas UK is a non-specific plasminogen activator. The activation of proUK to UK occurs physiologically only during the course of fibrinolysis.

The importance of uPA in intravascular fibrinolysis has often been overlooked because it was mistakenly believed to be only an extravascular plasminogen activator. This was in part related to uPA having no fibrin affinity and instead having an affinity for a cell receptor. However, it is now abundantly clear that uPA has an important, if not dominant function in intravascular fibrinolysis.

The biological system of endogenous fibrinolysis is initiated by tPA released from its storage site in the endothelium of the vessel wall at the site of an intravascular fibrin thrombus. Due to tPA's high fibrin affinity it binds to its binding site on residues γ' (312-325) on the D-domain of intact fibrin [2,3]. This site is proximal to a fibrin bound plasminogen on Lysine A α 157 forming a ternary complex [4]. This complex promotes tPAs plasminogen-activating activity 1,000-fold [5] and initiates fibrin degradation. Since tPA has no other known fibrin binding sites, its fibrin-dependent lytic activity is limited to this step, and the remaining two steps of fibrinolysis are by uPA.

Sequential activation of fibrin-bound plasminogens is more effective

The initiation of fibrin degradation by tPA creates new plasminogen binding sites [6] which are two in number [7]. The first of these is a triple terminal lysine binding site on the fibrin E-domain that enables the intrinsic activity of proUK to activate it. Against this conformation, the activity of proUK is equal to that of UK [8]. Activation of this plasminogen is associated with reciprocal activation of proUK to UK [9] and UK then activates the remaining fibrin-bound plasminogen completing fibrinolysis. Therefore, fibrinolysis involves the activation of three fibrin-bound plasminogens of which tPA activates the first and uPA (proUK/UK) the remaining two.

The activators tPA and proUK have complementary mechanisms of action and their combined effects are synergistic [10], both in vitro [11] and in vivo [12]. Furthermore a sequential administration of the



activators, as in the biological sequence, induced twice as rapid clot lysis as a simultaneous administration [13].

Sequential administration of the activators is also safer

Fibrin-specific and safe fibrinolysis is predicated on the activation of fibrin-bound plasminogen and the sparing of free plasminogen. In this way plasminemia is avoided keeping clotting factors I, V, and VIII from being degraded, thereby maintaining normal hemostasis. The other source of bleeding during fibrinolysis is due to tPA's fibrin affinity not distinguishing between fibrin in a clot and hemostatic fibrin. Therefore, bleeding from lysis of hemostatic fibrin can occur but this risk can be minimized by avoiding an iv infusion of tPA and limiting it to a small bolus. This is all the tPA needed when the sequential system of activator administration is used. The plasma half-life of tPA is only 5 minutes and the proUK administration can be delayed until after the tPA has been eliminated or inhibited.

By contrast fibrinolysis by monotherapy is less effective and risky

Standard fibrinolysis by tPA monotherapy can only activate the first plasminogen which is the one in the ternary complex. The other two fibrin-bound plasminogens are inaccessible and can only be activated by high, non-specific doses at which tPA is only a weak activator. Furthermore, at these tPA doses bleeding due to the lysis of hemostatic fibrin by tPA occurs.

Therefore, fibrinolysis by tPA alone is neither effective nor safe. Not surprisingly, it has been replaced by PCI as the treatment of choice for AMI. Unfortunately, for ischemic stroke fibrinolysis with tPA or one of its derivatives is currently the only option.

Scientific progress requires paradigm shifts

Since the above description is just as obvious as it seems, what has held up progress in this field? The science philosopher, Thomas Kuhn, showed that "Science does not progress as a linear accumulation of new knowledge, but undergoes periodic revolutions called paradigm shifts." The paradigm shifts tend to be resisted resulting in scientific progress being delayed. This has occurred in fibrinolysis where tPA has been the only plasminogen activator since it was first approved in 1987. It became synonymous with fibrinolysis so that publications on fibrinolysis do not mention the activator used since it was assumed to be tPA. As a result, when tPA failed to live up to expectations and was replaced by a catheterization procedure, fibrinolysis in general became discredited alongside tPA.

Fibrinolysis has been discredited before it was understood

Fibrinolysis by tPA alone was discredited for good reason, but the fibrinolysis baby should not have been thrown out with the tPA bath water since tPA and fibrinolysis were wrongly equated.

As reviewed above, tPA's fibrin-specific function is limited to the initiation of fibrinolysis, which constitutes one-third of lysis. The remainder requires uPA, both proUK and its activated form UK. To abandon fibrinolysis before it has been understood and developed according to the natural fibrinolytic paradigm is a serious error. This is made especially apparent when the results of a clinical trial using the sequential combination are included.

Clinical validation of fibrinolysis by both activators administered sequentially

A sequential administration of the two activators was once tested in 101 patients with AMI. In the first 10 patients, a 10 mg bolus of tPA was given to initiate lysis, which turned out to be excessive and so only

a 5 mg bolus (5% of the standard tPA dose) was given to the remaining 91 patients. This was followed by an infusion of proUK, 40 mg/h for 90 minutes [14]. This combination induced a TIMI-3 patency at 24 h 82% of the 28 patients re-catheterized at that time, the overall mortality was 1% [15]. This compares favorably with the best results in the tPA trials in which the TIMI-3 patency at 24h was 45% and the mortality was 6.3% [16,17].

Therefore, 5 lives per hundred could be saved by adopting this sequential fibrinolytic regimen. Had this been done at the time this data was first published, almost one million AMI deaths in the US alone could have been saved.

Conclusion

Prompt reperfusion of a thrombus blocked artery is essential for optimal salvage of heart or brain function and for the lowest mortality. This is possible only with fibrinolysis. Fibrinolysis has been induced only with tPA, which is inadequate and, therefore, was replaced by a vascular procedure whenever possible. Since these are hospital procedures, reperfusion is significantly delayed undermining its potential benefit. Fibrinolysis is the only means by which prompt reperfusion can be achieved. For this, fibrinolysis must be rehabilitated using the sequential administration of both activators according to the natural fibrinolytic paradigm. By this means, patients with thrombo-occlusive disease can be reperfused within 1-2 hours when the lowest mortality and greatest salvage of function is possible.

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