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Fibrinolysis and Fibrinolytic Therapy

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Commentary

Fibrinolysis is our natural defense against the build-up of clots (fibrin) that are needed to stem bleeding and are required for the repair of the daily wear and tear injuries to the vascular system. The activity of fibrinolysis can be generated either on the cells which express profibrinolytic receptors or the surface of fibrin containing thrombus. Fibrinolysis is rigidly controlled by inhibitors, cofactors and receptors. Fibrinolytic therapy utilizes this system to treat disorders like heart attack and most strokes, which are caused by large clots that obstruct an artery to a portion of the heart or brain. Unfortunately, due to a misunderstanding of natural, biological fibrinolysis, only one of the two activators that are integral to this system, tPA and uPA, have been used in therapy. Not surprisingly, fibrinolysis with tPA alone has been of disappointing efficacy and associated with bleeding complications, including intracranial bleeding.

For this reason, over the past decade, instead of correcting this error, fibrinolytic therapy has been largely rejected and replaced by angioplasty, which has become the treatment of choice for a heart attack. Since this is a technically complex catheterization procedure, it is time-consuming, costly and requires hospitalization. As a result, restoration of circulation is almost invariably delayed beyond the time at which optimal salvage of heart or brain function is possible, which is 1-2 h after the event [1]. Restoration of blood flow within this time period is possible only with fibrinolytic therapy for most patients. To make fibrinolytic therapy both effective and safe, nature's model needs to be followed, which means using both tPA and uPA in a sequential combination.

When tPA and uPA were once administered as in the biological model, and given to 101 patients with heart attack, complete (TIMI-3) opening of the coronary artery responsible for the infarct was almost double that achieved in the best of the tPA studies, and the mortality was reduced 6-fold over tPA [2]. Despite publication of these findings in the leading cardiology journal, this highly successful study received little attention at the time, such was the conviction that tPA was the only activator in fibrinolysis. This idea was in large part due to uPA in blood being carried on the surface of certain cells, platelets and monocytes, where it was undetected [3,4], rather than being free in blood plasma where tPA is found. No second study using both tPA and uPA was ever undertaken, and uPA development was abandoned by the industry.

More recently, a single site mutant of uPA was developed which is better adapted to therapeutic use than was native form of uPA, prouPA. This is because the latter is unstable in plasma at therapeutic concentrations. This mutant prouPA will be used in a sequential combination following a mini bolus of tPA (5% of its standard dose), as in the above study. Clinical trials (phase-2) with this sequential combination in heart attack and stroke are scheduled for the second half of this year. Repeats of the results in the latter results [2] are anticipated.

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