Newer Thrombolytic Agents

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Abstract

Several lines of research towards improvement of thrombolytic agents are being explored, including the construction of mutants of plasminogen activators, chimeric plasminogen activators, conjugates of plasminogen activators with monoclonal antibodies, and plasminogen activators from animal or bacterial origin. Some of these new thrombolytic agents have shown promise in animal models of venous or arterial thrombosis; only those which are being investigated in clinical studies are briefly discussed.

Monteplase is a modified tissue type-plasminogen activator (t-PA) constructed by substituting only one amino acid in the epidermal growth factor domain ($Cys^{84} \rightarrow Ser$) and expressed in baby Syrian hamster kidney cells. It has a prolonged half-life of more than 20 min, as compared to 4 min for native t-PA. TNK-t-PA differs from t-PA by 3 mutations. This mutant has increased thrombolytic potency, slower clearance and enhanced resistance to the inhibitor PAI-1. Reteplase is a non-glycosylated deletion mutant of wild-type human t-PA which contains only kringle 2 and the protease domain but lacks its kringle 1 and the finger and growth factor domains. The structural changes in reteplase translate into a decreased fibrin binding, a lower affinity to endothelial and liver cells resulting in an extended half-life. Lanoteplase is a deletion mutant of t-PA with a half-life that is circa 10 times greater than alteplase, making it suitable for single bolus injection. YM866 is another mutant of t-PA in which the aminoacids 92 to 173 of kringle 1 were deleted and arginine^{275} replaced by glutamic acid which confers a longer half-life to the mutant. Recombinant glycosylated prourokinase has a greater stability than recombinant unglycosylated pro-urokinase, is rapid acting and safe in the clinical doses used. Staphylokinase (SAK) is produced by* **Staphylococcus aureus. It induces efficient and rapid recanalization, also after bolus injection, but is immunogenic.***

There are only a few large scale clinical trials published directly comparing fibrin-selective thrombolytic drugs. In patients with acute myocardial infarction, reteplase, administered in bolus injections, is associated with a similar mortality and bleeding rate as front loaded t-PA. Bolus TNK-t-PA has a similar incidence of cerebral bleeding as front loaded t-PA and is associated with the same survival rate after acute myocardial infarction in a large mortality trial.

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