Pharmacokinetics of the Recombinant Thrombolytic Agents

What is the Clinical Significance of Their Different Pharmacokinetic Parameters?

Adam Cohen
Leiden University Medical Centre, Centre for Human Drug Research, Leiden, The Netherlands

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Abstract

In addition to the first generation thrombolytics streptokinase and urokinase there are now a number of new human thrombolytic proteins produced by recombinant techniques. In this review alteplase, saruplase and reteplase are discussed.

These compounds differ with respect to their pharmacokinetics. Alteplase and saruplase have relatively short half-lives and are high clearance compounds. Their clearance is dependent upon the hepatic blood flow. This is relevant as myocardial function strongly influences liver blood flow and hence the clearance of alteplase and saruplase. The clearance of reteplase is less dependent upon liver blood flow and is partly dependent on renal excretion. This extends its half-life and reteplase has been successfully administered as a double bolus injection.

The question remains if these differences are responsible for any clinical benefits that could not be accomplished by variations in dosage or dosage schedule for a single thrombolytic. Pharmacokinetic differences can only be interpreted if reasonable knowledge exists about the shape and location of the plasma concentration- (adverse) effect curves.

This information is not yet available for the recombinant thrombolytic drugs and any clinical differences could well be caused purely by differences in dosage or dosage schedule. It is recommended that plasma concentrations of thrombolytics are measured in future clinical trials, for which techniques are currently available.
All thrombolytic agents open coronary arteries and reduce mortality after myocardial infarction. After this was shown for the archetypal thrombolytic streptokinase, a number of newer agents with different pharmacodynamic properties were produced by recombinant DNA techniques. Subsequently, considerable disputes occurred over the superiority of individual agents over each other in their ability to open coronary arteries, reduce mortality and induce adverse events, notably intracerebral bleeding. The discussion has been mainly centred around the pharmacodynamic properties of the agents and only recently has dosage or pharmacokinetics been taken into account.

This review takes the pharmacokinetic differences between the different thrombolytic agents as a starting point to evaluate if these may influence the differences in clinical outcome. The new thrombolytics (produced by recombinant techniques) are considered only if enough evidence is available to evaluate both the pharmacokinetics in humans and clinical outcome. This review therefore is limited to alteplase (recombinant tissue-type plasminogen activator; rt-PA), saruplase (recombinant single-chain urokinase plasminogen activator; rscu-PA) and reteplase.

1. Pharmacodynamics of Thrombolytic Drugs

The biochemical cascade that underlies the actions of all thrombolytics is shown in figure 1 and has been authoritatively reviewed. The main message from this diagram for the purpose of this review is that the relationship between the plasma concentrations and the final effect of any thrombolytic drug may be subject to a multitude of other factors than the plasma concentration per se. However, the therapeutic use of thrombolytics induces supraphysiological concentrations of the proteins in the blood and many of the endogenous inhibitors.