Thrombolytic and profibrinolytic agents have been found to exhibit varying degrees of interactions with heparin, low molecular weight heparins (LMWHs), prostacyclin and cyclooxygenase inhibitors. Our initial in vivo studies did not reveal significant synergistic effects between the lytic agents and the above drugs. To study the in vivo effect of these interactions a primate (Macaca mulatta) model was employed. Initially, the relative fibrinolytic and/or profibrinolytic efficacies of t-PA (American Diagnostica) were evaluated in normal and hypercoagulable primates (homologous serum treated) in terms of both the consumption of plasminogen, as antifibrin and fibrinogen, and the formation of FDP, D-Dimer and NO+42 related peptides. Subsequently, studies IV and 50 pretreatment of the animal with a LMWH CY 222 (Choay) at 1 mg/kg, followed by administration of t-PA (3000 ug/kg IV), resulted in a marked decrease in fibrinolytic effects with a prolongation of the bleeding time. The results with CY 222 pretreatment followed by streptokinase (2500 IU/kg IV) or urokinase (2500 IU/kg IV) administration were similar but less dramatic. In this model, t-PA also showed synergistic interactions with urokinase and protein C concentrate. Pretreatment of primates with varying doses of urokinase and protein C prior to t-PA administration resulted in a marked decrease of anti-tPA titre and a slight increase in antigenic and functional t-PA. The augmentation in t-PA activity by these thrombolytic agents may be due to the exposure of various regulatory fibrinogen/fibrin related peptides or the generation of endotheilial release products. The mechanism of LMWH induced synergism of thrombolytic agents may also involve the release of endotheilial t-PA or a reduction of modulatory plasma proteins. Although preliminary, these observations suggest that thrombolytic/profibrinolytic agents exhibit varying degrees of drug interactions with themselves and with antithrombotic agents. Preclinical knowledge of these interactions may be of value in the design of effective therapy or modification thereof. Furthermore, drug interactions with thrombolytic/profibrinolytic agents should be taken into account to optimize safety/efficacy of these agents on an individual basis.

Effect of Different Heparins on Thrombolysis with t-PA and scu-PA in Rabbits with Experimental Thrombosis

The results presented indicate that at sufficiently high doses, heparin and heparinoids significantly enhance thrombolysis with t-PA and scu-PA in a rabbit model of thrombosis. The administration of heparin or low-M heparin fractions in animals with experimental thrombosis or in patients with thromboembolic disease may result in a significant reduction of the thrombus size, without being associated with measurable changes in the blood fibrinolytic parameters. The measured effect of clinical-grade heparin (hep) and two low-M heparin fractions (CY216 and CY222 from Choay, Paris, France) on thrombolysis with t-PA and with scu-PA in a rabbit jugular vein thrombosis model (Collen et al., J. Clin. Invest. 71, 369, 1983). After thrombus formation, t-PA (0.25 mg/kg) or scu-PA (0.5 mg/kg) were infused overnight. The heparins were administered at hourly intervals at the start and during the infusion as bolus injections of the following amounts (expressed in anti-Xa units): Hep: 70 (A) or 200 (B); CY216: 30 (A) or 90 (B); CY222: 50 (A) or 150 (B). Results were (mean ± SEM).

Thrombolysis (percent):