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THROMBELASTOGRAPHIC EVALUATION OF THE EFFECT OF ADDED PLASMINOGEN TO PLASMA ON FIBRINOLYSIS USING VARIOUS FIBRINOLYTIC ACTIVATORS. L. Summaria, G.P. Yang, D.S. Holloway, and J.A. Caprini. Evanston Hospital, Evanston, IL, and Northwestern University Medical School, Chicago, IL, USA.

When lysis of peripheral thrombi requires infusion of plasminogen activators for longer than 24 hours duration, slow resolution of an obstructive thrombus can result in tissue injury and loss of limb. This study evaluated the effects of increasing the plasminogen concentration on the kinetics of clot lysis induced by plasminogen activators. By adding varying concentrations of any plasminogen activator to plasma, clot lysis can be continuously monitored using thrombelastography (TEG). Parameters measured during the lysis portion of the pattern are the final amplitude reached (A_∞), various time parameters (T, T' and $T_{50\%}$), and the absolute change in amplitude (ΔA). By adding different amounts of Lys-Plasminogen (LYS-PLG) to plasma, we were able to measure the effect of added LYS-PLG on the lysis pattern with different activators (streptokinase, the plasminogen-streptokinase complex, or the B-chain-streptokinase complex). Statistical analysis of the plots of $T_{50\%}$ (time for 50% lysis, where the TEG amplitude is reduced to half that of the maximum amplitude) versus LYS-PLG concentration showed that a second order polynomial regression gave R values of better than 0.969. The addition of a small amount of LYS-PLG (20% of the normal plasma concentration) resulted in a two-fold decrease in $T_{50\%}$ with all activators. Maximum clot-lysis enhancement was reached when 60% excess LYS-PLG was added. This amount caused a 2.9 to 3.9 fold decrease in $T_{50\%}$. Values above 60% did not significantly reduce clot- lysis time any further when very low levels of plasminogen activator were added to plasma. Plots of clot-lysis ($T_{50\%}$) versus activator or LYS-PLG concentration showed that the amount of activator could be decreased by at least two-fold if between 40 to 60% extra LYS-PLG is added.

Thus, the addition of LYS-PLG to a plasma clot produced a two- to three-fold increase in the rate of clot lysis (2 to 3 fold decrease in $T_{50\%}$) or permitted a two-fold lesser amount of activator to produce the same lysis pattern.

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COMPARISON OF A BOLUS AND A INFUSION DOSE REGIMEN OF RECOMBINANT TISSUE TYPE PLASMINOGEN ACTIVATOR (rt-PA) ON THE RATE OF THROMBOLYSIS IN THE RABBIT JUGULAR VEIN MODEL (RJVM). C.J. Refino, B. Hultgren, S. Hollenbach, and A. Hotchkiss. Genentech Inc. South San Francisco, CA, USA

The success of intravenous infusion of rt-PA in the treatment of myocardial infarction, along with new applications in deep vein thrombosis and pulmonary embolism has stimulated interest in optimizing dosage regimens. Dosage strategies should be tested in a relevant animal model before clinical use. In the RJVM, net lysis is calculated from the difference in I-125 fibrinogen present in a rabbit jugular vein thrombus, pre and post thrombolytic therapy, therefore changes in the rate of lysis would not be detected. To continuously monitor rates of lysis in the RJVM, a flat surface gamma detector probe was secured over the jugular vein thrombus of the anesthetized rabbit, and Gamma counts were accumulated for one minute, at 10 minute intervals. Rates of lysis and net lysis were calculated from these data. Net lysis was also determined by the traditional method in order to validate the new technique. Using this experimental design we compared the efficacy of a bolus (0.4 mg/kg over 1 min) to an infusion (0.4 mg/kg over 2 hours, 10% given as an initial bolus). A control group received an infusion of rt-PA excipient. The bolus group was terminated at 60 minutes, since there was no detectable lysis in any of these animals after 30 mins. There was an excellent correlation between the net lysis calculated either by the probe or the traditinal procedure (Y = 1.0 x -2.8, r = 0.88). The lysis rates were:

rt-PA Dependent Rates of Lysis (% Lysis/Hour S.D.)

	Bolus	Infusion	
-10 to 0 min	0	0	
0 to 30 min	17 ± 12	18 ± 23	p>0.5
30 to 120 min	0 ± 2	7 ± 2	p<0.01

Lysis rates were linear during the specified time intervals.

From these data we conclude that in the RJVM a bolus of rt-PA offers no clear advantage in efficacy over a comparable dose given as a 2 hr infusion. This observation appears to hold true even during the first 30 minutes of treatment where any advantage the bolus might have would most likely be evident.

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SHORT-TERM LYSIS BY ULTRAHIGH STREPTOKINASE TREATMENT IN CHRONIC ARTERIAL OCCLUSIONS AND ACUTE DEEP VENOUS THROMBOSIS. M. Martin (1) and B.J.O. Fiebach (2). Geriatric Dept. (1) and Radiology Dept. (2), Städtische Kliniken Duisburg, West Germany.

171 chronic arterial occlusions and 86 acute venous thromboses were treated by systemic ultrahigh streptokinase (UHSK) infusions. 38% of the patients were over 65, 27% over 70 years of age. The UHSK scheme consisted of a 1.5 million units SK per hour maintenance infusion over a period of 6 hours. 46% of the patients received one, 47% two, 6% three, and 1% four series (one series per day). 81% of the arterial patients had a history of less than 3 months. In 54% of the cases PTA followed UHSK treatment for dilation of a residual stenosis or removal of occlusion residues still persistent. In the venous patients the most proximal location was distributed as follows: calf veins 1%, femoral vein 57%, iliac vein 28%, subclavian vein 14%. The average thrombosis history was 8 days.

Clearance rates of chronic arterial occlusions

Regimen	Aorta	Iliac artery	Femoral artery
UHSK alone	2/3	20/32 = 63%	48/136 = 35%
UHSK+PTA	-	22/32 = 69%	68/136 = 50%

By setting up of sub-groups more favorable results were calculated. For exemple, a femoral occlusion group consisting of cases with a history shorter than 6 weeks and 2 or 3 calf arteries patent displayed a clearance rate of 77%, a figure much higher than the overall femoral result.

Clearance rates of deep venous thrombosis

Total clearance	Partial clearance	No success
35/86 = 41%	39/86 = 45%	12/86 = 14%

The thrombosis duration played a significant role for thrombosis dissolution. The average occlusion history was 6 days in the total clearance group compared with 12 days in the unsuccessful cohort.

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COAGULATION CHANGES UNDER THREE DIFFERENT DOSAGE REGIMENS OF SINGLE-CHAIN UROKINASE TYPE PLASMINOGEN ACTIVATOR. R.Zimmermann, A.Horn, C.Bode, J.Harenberg, G.Schuler, F.Schwarz, H.Tillmanns, W.Kübler, Medizinische Universitätsklinik, 6900 Heidelberg 1, GFR

Therapy with streptokinase and urokinase induce effective thrombolysis but may be complicated by hemorrhagic side effects. In order to minimize these complications single-chain urokinase-type plasminogen activator (scu-PA) was given in patients with acute transmural myocardial infarction at three different dosage regimens consecutively in combination with heparin. In a first group four patients received 15 mg, thirteen 48 mg (group II) and five 72 mg (group III) of scu-PA intravenously. In 22 cases detailed clotting analyses could be performed. Results: The coagulation analysis demonstrated a reduction of the fibrinogen concentration by 11 % in group I, 17 % in group II and 44 % in group III. Plasminogen decreased by 9 % in the first, 43 % in the second and 61 % in the third group. The level of α_2-antiplasmin showed a reduction of 12 % in group I, 48 % in group II and 80 % in group III. Fibrin degradation products increased in all groups. The euglobulin clot lysis time was moderately shortened in group I but significantly in the groups II and III. Reptilase and thrombin coagulase time were prolonged moderately. Thrombin clotting time and aPTT could be attained at therapeutic range by additional application of heparin. Antithrombin III showed no alteration. Thrombolysis could be achieved in none of the patients in group I but with good results in group II and III.

Our data suggest that intravenous application of scu-PA at a dosage of 48 mg is able to induce effective thrombolysis with only slight destruction of fibrinogen. At higher dosages a further increased rate of thrombolysis may be possible but also a higher rate of fibrinogenolysis may be considered.