944

RELATIONSHIP BETWEEN BLEEDING EVENTS AND CHANGES IN PLASMA IN PATIENTS TREATED WITH RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR AND STREPTOKINASE IN TIMI STUDY-PHASE I. A.K.Rao MD, for TIMI Investigators, Temple University, Philadelphia, PA, U.S.A.

In Thrombolysis in Myocardial Infarction (TIMI) trial (Phase I) patients were randomized to receive intravenously either 80 mg of predominantly double-chain (G11021) recombinant tissue plasminogen activator (rt-PA) over 3 hrs or 1.5 million units of streptokinase (SK) over 60 min. All patients received an intravenous heparin bolus (5000 units) prior to angiography and a continuous infusion (1000 units/hr) starting 3 hr later. Bleeding occurred in 33% (rt-PA) and 31% (SK) of patients; over 70% of episodes were at vascular puncture sites. We report here the relationship between bleeding events and changes in plasma fibrinogen (FBG), plasminogen (PMG), and fibrin(ogen) degradation products (FDP) at 5 hr after initiation of drug infusion. Shown are number of patients with hemorrhage, total number of patients, and correlation coefficients (r) for occurrence of bleeding versus the changes in plasma proteins in each group.

		rt-PA Patients(%)	SK Patients(%)
FBG	> 250 mg/dl	16/55 (29%)	3/13 (23%)
	150-249 mg/dl	13/49 (26%)	11/38 (29%)
	0-149 mg/dl	12/20 (60%)	22/68 (32%)
		r = -0.16 (p=0.07)	r= -0.08 (p=0.39)
PMG	> 50 %	7/30 (23%)	0/2 (0%)
	20-49 %	31/88 (35%)	4/22 (18%)
	0-19 %	2/5 (40%)	32/98 (33%)
		r = -0.17 (p=0.06)	r= -0.18 (p=0.04)
FDP	0-99 µg/ml	12/60 (20%)	0/7 (0%)
	100-399 µg/ml	15/56 (45%)	19/78 (24%)
	> 400 µg/ml	3/5 (60%)	17/35 (48%)
		r= 0.282 (p=0.002)	r= 0.270 (p=0.003)

The data indicate a relationship between bleeding events and changes in plasma proteins, with higher frequency of bleeding in patients with greater changes. FDP levels in both groups show a correlation with bleeding unlikely due to chance alone. While the hemorrhage may be due to multiple factors such as vigorous anticoagulation, arterial punctures, and platelet inhibition, the above findings suggest that the plasma changes contribute to the hemorrhagic events.

945

CORONARY THROMBOLYSIS AND PREVENTION OF REOCCLUSION WITH RECOMBINANT DOUBLE CHAIN TISSUE PLASMINOGEN ACTIVATOR. R. Kent for the Wellcome Tissue Plasminogen Activator Study Group. Wellcome Research Laboratories, Research Triangle Park, NC, U.S.A.

The dose response (DR) of tissue plasminogen activator (t-PA)in patients (pts) with acute myocardial infarction (AMI) and the efficacy of 4-6 hr maintenance infusions (M) of t-PA in preventing early reocclusion (R) have been reported in small numbers of pts. No studies have determined the efficacy of longer M in limiting short term R. In two related trials we examined DR and long term M in a large number of pts. We administered a uniform t-PA product [>98% double chain (DC)] to 223 pts 3.1 ± 1.1 hrs after the onset of AMI. Pts received 0.25 - 0.95 megaunits (MU)/kg/90 min and then underwent coronary angiography (CA): Responders were defined by TIMI grades 2 or 3. Results were.

Dose (MU/kg/90 min)	Response Rate at 90 min
0.25-0.34	57% (25/54)
0.35-0.44	63% (52/82)
0.45-0.54	73% (44/60)
0.55 and above	85% (23/27)

In a logistic regression anaylsis the coefficient for dose was significant ($p<0.02$). Two subsets of the above pts received M. Groups A (41 pts) and B (51 pts) had received 0.26 - 0.40 and 0.41 - 0.54 MU/kg/90 min respectively. 66% of A and 78% of B were responders, received an additional 90 min of t-PA at 1/3 the initial rate and then 1 of 4 M for 9-21 hrs (mean total 17.2 ± 4.5 hrs) at which time CA was repeated. Results for A + B were:

M Dose (MU/kg/hr)	Reocclusion Rate
0.012-0.018	11% (3/27)
0.026-0.035	18% (3/17)
0.041-0.047	0% (0/13)
0.049-0.062	14% (1/7)

For all pts fibrinogen decreases were mild. Bleeding was primarily related to vascular invasion and M length. We conclude that the DR for DC tPA can be accurately defined and long term M to limit short term R are feasible. Future studies may define t-PA dosing regimens suited for specific clinical situations.

946

THE ISRAELI STUDY OF EARLY INTERVENTION IN MYOCARDIAL INFARCTION; INTRAVENOUS RT-PA WITH SUBSEQUENT REVASCULARIZATION. G.I. Barbash, H. Hod, H.I. Miller, A. Roth, S. Rath, Y. Har Zahav, B. Rabinovitz, S. Laniado & U. Seligsohn. Cardiology and Hematology Dept. Sheba and Tel-Aviv Medical Centers, Israel.

Immediate mechanical revascularization for large population of acute myocardial infarction (AMI) patients, is logistically impractical. Effectiveness of early intravenous rt-PA, and feasibility of delaying the coronary angioplasty were studied. 57 AMI patients were enrolled since October 1986; 30 via Emergency ward, and 27 via mobile intensive care unit. The mean time interval from onset of ischemic pain to rt-PA bolus was 115+52 min. The protocol included an initial 10 mg rt-PA bolus followed by continuous infusion of 110 mg over 6 hr, concomitant continuous heparin and lidocain infusion, and aspirin 250 mg/day; coronary catheterization after 72 hr. and angioplasty of suitable infarct-related artery (IRA). 49 patients (86%) had clinical signs of reperfusion (disappearance of chest pain with resolution of ST elevation) within 60 min. The 8 "non-responders" were treated earlier (shorter time interval from onset of pain to rt-PA bolus) than the "responders" (87+37 and 120+53 min respectively,p=0.01). Of "responding" patients, 5 had intermittant reocclusion-reperfusion cycles, and an additional 4 reoccluded silently before coronary catheterization (7 to 72 hr). 29 PTCA successful procedures (53% of pats) of the infarct-related artery (IRA) were performed: 25 during the protocol catheterization at 72 hr, and 4 which were performed as an emergency procedure of high grade stenosis (1), or totally occluded IRA (3), in 4 of the 8 "non-responders". There were 3 emergency and 8 elective bypass operations (20%). While in the 25 patients with anterior wall infarction the admission Lt. ventricular ejection fraction (LVEF) (37+12%) improved (46+17%) at discharge, in the 30 patients with inferior wall infarction the admission and discharge LVEF were both normal. Two patients expired; one within minutes after treatment initiation, and the other following no response to the thrombolytic therapy and reocclusions of repeat coronary dilatations. These results indicate that rt-PA thrombolysis is a safe treatment modality enabling planning of deferred mechanical revascularization under more optimal conditions.

947

RESULTS OF COAGULATION-FIBRINOLYSIS ANALYSES IN 386 PATIENTS WITH ACUTE MYOCARDIAL INFARCTION TREATED WITH RECOMBINANT TISSUE-TYPE PLASMINOGEN ACTIVATOR (rt-PA) (TAMI TRIAL). D.C. Stump (1), E.J. Topol (2), R. Califf (3), A.B. Chen (4), A. Hopkins (4) and D. Collen (1). Univ. Vermont, Burlington, VT (1), Univ. Michigan, Ann Arbor, MI (2), Duke Univ., Durham, NC (3) and Genentech, So. San Francisco, CA (4) U.S.A.

Three hundred eighty-six patients with acute myocardial infarction received up to 150 mg rt-PA (single chain) IV either over 8 h (60 mg over 1 h, 20 mg/h for 2 h, 10 mg/h for 5 h) (173 pts) or over 5 h (1 mg/kg over 1 h, remainder over 4 h) (213 pts), before randomization to early or late angioplasty. Blood was collected on a lyophilized mixture of citrate and the t-PA inhibitor D-Phe-Pro-Arg-CH_2Cl (PPACK), to maximally prevent in vitro fibrinolytic activation and concomitant fibrinogen degradation. The plasma rt-PA level increased to 2.4 ± 2.0 µg/ml (mean ± SD) and 1.7 ± 1.3 µg/ml after 3 h and to 1.0 ± 1.8 and 1.0 ± 0.9 µg/ml at the end of the infusion. Fibrinogen levels (coagulation rate assay) fell to 58 ± 28 and 52 ± 27% at 3 h and to 53 ± 28 and 47 ± 26% at the end of infusion. Fibrinogen degradation products increased to 32 µg/ml (median, with 10 and 90 percentile values of 2 and 512 µg/ml) after 3 h and to 32 µg/l (median, with 10 and 90 percentile values of 2 and 512 ug/ml) at the end of infusion. The fibrinogen decreased to below 1 g/l in 23% of patients and below 0.5 g/l in 11% after 3 h infusion with corresponding values of 33% and 12% at the end of infusion. Thus, at the infusion rates required for rapid coronary artery reperfusion in man, rt-PA remains relatively fibrin-specific. The cause of the extensive fibrinogen depletion occurring in some patients remains to be further investigated.