175

A RANDOMISED DOSE RANGING STUDY OF TWO-CHAIN TISSUE-TYPE PLASMINOGEN ACTIVATOR (BW-t-PA) IN MYOCARDIAL INFARCTION: IN VITRO MONITORING. C. Kluft (1), A. McNeill (2), A.A.J. Adgey (2), D.C. Rijken (1), W. Nieuwenhuizen (1), A.F. Cohen (3). Gaubius Institute TNO, Leiden, the Netherlands (1), Royal Victoria Hospital, Belfast (2) and Wellcome Research Labs, Beckenham, UK (3).

In a randomised study, thirty patients with myocardial infarction received either 20, 50 or 100 mg recombinant BW-t-PA in 90 minutes. Blood samples were taken just before the infusion, and after 90 min. In vitro effects of t-PA were prevented by addition of 250 µg/ml polyclonal t-PA antibodies, which were shown to block in vitro actions of up to 5 µg t-PA/ml during plasma handling.
There were dose related (MIU/kg/90 min) decreases of α_2-antiplasmin (AP, functional assay), plasminogen (PLG, streptokinase assay) and fibrinogen (FBG, Clauss) at 90 min (lineair regression: r = 0.67; 0.55 and 0.40, n = 30, all $p < 0.05$, resp.). Decreases for the 100 mg dose were for the respective components: 70 ± 10 (SD)%, 28 ± 7% and 33 ± 17% of pretreatment levels. The extent of the AP changes appeared to be the most sensitive parameters and these changes correlated with those in PLG and FBG. Pretreatment values of FBG were elevated (137 ± 37%) and at 90 minutes were 100 ± 23% of pooled plasma. Decreases in FBG were significantly ($p < 0.001$) correlated with absolute pretreatment levels, indicating preferential reductions of elevated levels of fibrinogen.
Using our new enzymimmunoassays based on monoclonals for degradation products of fibrinogen (FDP), fibrin (FbDP) and the total (TDP), these products were measured in plasma (not serum). Before infusion 14 patients showed TDP levels (range: 0.5 - 2.3 µg/ml); at 90 min 29 patients (0.6 - 13 µg/ml. The increase in TDP accounted for only 0.75% (range up to 5.3%) of the apparent FBG reduction (Clauss) at 90 min. Detectable FbDP were generated in 24 patients at 90 min. For the two highest dosages the level (median 2.0 µg/ml) was significantly higher than at the dosage of 20 mg (median 0.85 µg/ml), indicating weaker fibrinolytic effect of t-PA at the lowest dosage. To evaluate the fibrinolytic/fibrinogenolytic effects of the t-PA the ratio FbDP/FDP was calculated. For the 50 mg dosage all ratios were ≥ 1; for 100 mg only 6 patients showed a ratio ≥ 1 at 90 min. This may indicate relative specific increase of fibrinogenolysis at higher dosages.

176

A RANDOMISED DOSE RANGING STUDY OF DOUBLE CHAIN TISSUE PLASMINOGEN ACTIVATOR (BW t-PA) IN ACUTE MYOCARDIAL INFARCTION: CLINICAL RESULTS. A.D. McNeill (1), S.R. Cunningham (1), R. Koster, C. Bucknall, C. Sponzilli, and K. Kluft. The Wellcome European Tissue Plasminogen Activator Study Group, Royal Victoria Hospital, Belfast, Northern Ireland (1).

Despite extensive experimental use of t-PA in patients with acute myocardial infarction (AMI) a randomised dose ranging study has not yet been published. Fifty-five patients were randomised to BW t-PA 20 mg, 50 mg or 100 mg administered over 90 minutes. They received the drug 2.3 hours (range 0.3-4.3 hours) after the onset of AMI and underwent coronary arteriography to determine perfusion grade of the infarct related artery at 90 minutes. Responders were defined by TIMI perfusion grades 2 or 3. Response rates were:

Dose (mg/90')	Dose (megaunits/kg/90')	Response rate
20	0.10-0.18	5/19 (26.3%)
50	0.19-0.67	11/18 (61.1%)
100	0.44-0.98	14/18 (77.7%)

A logistic model fitted to the data showed the probability of reperfusion to increase in a dose related manner to 70%. Fibrinogen concentrations were measured in 30 patients and decreased to 83.6% of the preinfusion value at 90 minutes after 20 mg, to 76.2% after 50 mg and to 67.1% after 100 mg. There was a significant correlation between the dose of BW t-PA in megaunits/kg and consumption of fibrinogen at 90 minutes ($p<0.05$). This study indicates that thrombolysis with double chain t-PA proceeds in a dose related manner and that systemic fibrinogenolysis appears to be mild.

177

CYCLES OF REOCCLUSION-REPERFUSION DURING RT-PA TREATMENT IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION (AMI). G.I. Barbash, H. Hod, S. Rath, Y. Har-Zahav, B. Rabinovitz & U. Seligsohn. Cardiology & Hematology Dept. Sheba and Tel-Aviv Medical Centers, Israel.

Early reocclusion of reperfused coronary arteries is observed in 20%-45% of AMI patients. Our protocol included: 10 mg rt-PA in bolus and continuous infusion of 50 mg in the 1st hr., 20 mg in the 2nd hr., and 10 mg during each of the following 4 hrs. Concomitantly, heparin 5,000 iu in bolus and continous infusion of 25,000 iu/24hr., and aspirin 250 mg/24hr were given. Five our of 49 patients who had clinical and electrocardiographic signs of reperfusion redeveloped severe chest pain and ST elevation while on 6 hr rt-PA and heparin. Increase of rt-PA infusion rate resulted, within 1-2 min., in resolution of chest pain and normalization of the ST elevation. 2-4 such cycles of reocclusion-reperfusion were observed in each case. In 2 out of these 5 patients stable reperfusion was achieved by administration of the 120 mg rt-PA infusion during 3.5 hr in one, and by repeated full dose protocol in the other. 2 underwent emergency percutaneous transluminal coronary angioplasty (PTCA), but kept reoccluding following several dilatations, and were eventually referred to an emergency bypass operation. 1 patient received the full protocol, but an infarction of the anterior wall was not prevented. Conceivably, there is a subset of patients with AMI in whom the present rt-PA regimen is insufficient, and higher total dose of rt-PA may be more effective.

178

BLEEDING COMPLICATIONS DURING RT-PA THROMBOLYSIS RELATED TO USE OF ANTI-INFLAMMATORY DRUGS PRIOR TO ACUTE MYOCARDIAL INFARCTION ADMISSION. A. Roth, G.I. Barbash, H.I. Miller, N. Keren, S. Laniado & U. Seligsohn. Cardiology & Hematology Dept. Tel-Aviv & Sheba Medical Centers, Israel.

Of 57 patients with acute myocardial infarction (AMI) treated with rt-PA, we observed 2 major bleeding complications, both in patients who had been treated with anti-inflammatory drugs prior to admission. The thrombolytic protocol included: 10mg rt-PA in bolus and continuous infusion of 110 mg over 6 hr, 5,000 iu heparin in bolus and continuous infusion of 25,000 iu/24hr, and aspirin 250 mg/24hr. The first patient, a 64 year old woman had been taking indomethacin 25 mg × 3 daily, during 3 weeks prior to the AMI. Rt-PA protocol was initiated with relief of chest pain and disappearance of ST elevation, but at 2 hr rt, sciatic pain developed. Treatment was continued according to protocol in spite of the pain, but on the 3rd day hemoglobin decreased to 7.8%. Abdominal CT scan disclosed retroperitoneal hemorrhage. All anticoagulant medications were stopped, and 4 units of blood were transfused. The retro-peritoneal mass dissolved gradually. The second patient, a 68 year old male was treated by diclofenac 100 mg for 5 days prior to admission for AMI, and consequently aspirin was removed from the rt-PA protocol. However, 2 hr after completion of the 6 hr rt-PA infusion, gross hematuria and a "coffee ground" vomiting developed. Heparin infusion was discontinued and antacid treatment initiated, resulting in cessation of bleeding within a few hrs. In both patients the anticipated prolongation of APTT (heparin) and about 30% decrease in fibrinogen level were observed as the sole abnormality, and thus we related the bleeding episodes to the anti-aggregating effect of indomethacin and diclofenac respectively. We suggest that the use of anti-inflammatory drugs prior to administration of rt-PA protocol can be hazardous, and that special prudence (possibly protocol modification) is warranted.