195

THE DEACYLATION OF P-ANISOYL PLASMINOGEN-STREPTOKINASE ACTIVATOR COMPLEX (APSAC, EMINASE™). H. Ferres, M.J. Hibbs and R.A.G. Smith. Beecham Pharmaceuticals Research Division, Epsom, Surrey, U.K.

The deacylation of the thrombolytic acyl-enzyme APSAC (BRL 26921) has been studied in various media using a radiochemical method. In a buffer containing glycerol, the half-life for deacylation at pH 7.4, 37°C was c. 20-50 min. depending on the concentration of APSAC. The concentration-dependence was found to be linked to the availability of free enzyme active centres during the deacylation process and could be normalised to about 50 min. by addition of inhibitors of plasmin or streptokinase. plasmin. In glycerol-free buffer, the deacylation half-life was 147 ± 5 min., indicating that glycerol, which is required to stabilise SK.Pm in activity-based assays caused artefactual acceleration of deacylation. In human plasma, the deacylation half-life was 104 ± 6 min. and was not concentration-dependent. In clotted human plasma, under conditions where APSAC was fibrin-bound, the deacylation half-life was 128 ± 10 min. which suggested that the deacylation process was not significantly influenced by binding of molecule to fibrin. The deacylation rate of APSAC in human plasma was similar to the plasma clearance rate at therapeutic doses in man (Been, M. et al., Int. J. Cardiol. 11 (1980) 53-61).

196

SYSTEMIC THROMBOLYSIS WITHIN THE FIRST 3 HOURS OF ACUTE CORONARY THROMBOSIS : APSAC VS STREPTOKINASE : A RAMDOMIZED STUDY

P. Monnier, U. Sigwart, F. Bachmann, C. Perret, L. Kappenberger - Division de Cardiologie, Soins intensifs et Hématologie, CHUV - 1011 Lausanne, Switzerland

Intravenous administration of thrombolytic agents in acute myocardial infarction may be preferable to intracoronary thrombolysis for practical reasons and to reduce time to reperfusion. As compared to the streptokinase infusion, the bolus injection of APSAC may be even more rational. We have therefore compared the effects of one intravenous bolus injection of APSAC (30 units in 5 min) to an intravenous injection of streptokinase (1.500.000 units in 60 min) within the first 3 hours (mean 141 min for APSAC and 135 min for streptokinase) after the onset of symptoms associated with acute myocardial infarction. All patients received i.v. heparin at therapeutic dosage for 24 hours starting 3-4 hours after the onset of therapy.
14 patients were randomized to the APSAC group and 11 to the streptokinase group. Coronary angiography carried dout 2.5 hours after beginning of treatment revealed a patency rate (complete opacification of the vessel at selective injection) of 92% (13 of 14 patients) for APSAC and 63% (7 of 11 patients) for streptokinase. Both thrombolytic agents produced similar fall in plasma fibrinogen levels. One death occurred in the streptokinase on day 4 due to rupture of the anterior ventricular wall. No other side effects were life-threatening, there consisted of local bleeding at the punction side. We conclude that APSAC is at least as efficient as streptokinase and easier to administer in patients with acute myocardial infarction.

197

COAGULATION STUDIES IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION DURING THROMBOLYTIC TREATMENT WITH APSAC (BRL-26921) OR STREPTOKINASE. J. Hoffmann (1), J. Bonnier (2) and J. de Swart (2) Departments of Clinical Laboratories (1) and Cardiology (2), Catharina Hospital, Eindhoven, the Netherlands.

We studied 70 patients with acute myocardial infarction in a multicenter trial comparing intravenous anisoylated plasminogen-streptokinase activator complex (APSAC or BRL-26921; 30 U in 2-4 min) with intracoronary streptokinase (SK; 250,000 U in 1 hour). Blood for coagulation and fibrinolytic determinations was taken before and 1½,12,24 and 48 h after thrombolytic treatment.
There were 65 patients in whom fibrinogen decreased by more than 10% of pretreatment; this was defined as a systemic lytic state. Of these patients,33 were treated with APSAC and 32 with SK. The lowest fibrinogen was found at 1½ h : about 15% and 22% of baseline, respectively. Also plasminogen and α2-antiplasmin reached low levels at 1½ hour. Plasminogen mean 32 ± 11 % and 34 ± 9% of pretreatment for APSAC and SK , respectively and α2-antiplasmin to less than 5% and 6 ± 9 %. Fibrin(ogen) degradation products peaked at 1½ h,too. The mean FDP was significantly higher in the APSAC group than in the SK group (739 vs. 355 mg/L). The global coagulation assays APTT, PT, TT and reptilase time all yielded comparable results: peak values at 1½h and no difference between both groups. After 24 to 48 hours all parameters had returned to their baseline levels, except FDP which was still elevated.
The euglobilin clot lysis time(ECLT) showed a different picture: after a very rapid decrease in both groups, ECLT quickly rose to normal in the SK group, but it remained shortened in the APSAC group at 24 and even 48 h. This sustained fibrinolytic activity was significantly different from SK.
In the 5 patients without systemic lytic state (3 APSAC; 2 SK), only minor changes in the parameters measured were found, except a decrease in ECLT at 1½ h in three of them and a slight drop in α2-antiplasmin in 2 patients. Two of these patients had a very high SK-resistance titer before treatment.
It is concluded that both APSAC and SK cause a profound systemic lytic state in the majority of patients, but the degree of this systemic lysis did not significantly differ between both groups. The total fibrinolytic activity, measured as ECLT, sustained for a significantly longer period in the APSAC group than in the SK group, which probably explains the low reocclusion rate of APSAC.

198

CARDIAC ENZYME RELEASE AFTER FIBRINOLYTIC THERAPY WITH INTRAVENOUS (i.v.) APSAC OR INTRACORONARY (i.c.) STREPTOKINASE IN ACUTE MYOCARDIAL INFARCTION. J.J.R.M. Bonnier, J.B.R.M. de Swart, J.J.M.L. Hoffmann. Catharina Hospital, Eindhoven, The Netherlands*.

The release of CK, CK-MB and ASAT in patients with acute myocardial infarction (AMI) was studied on the relation to reperfusion. In a randomized trial 85 patients with proven AMI entered the study. The occlusion of the infarct related vessel and reperfusion were all assessed angiographically. Fibrinolytic therapy with anisoylated plasminogen streptokinase activator complex (APSAC) i.v. or with streptokinase (SK) i.c. was started within 4 (mean 2.4) hours of the onset of symptoms. 42 were treated with a single i.v. injection over 3-5 min. of APSAC (30U) and 43 with an i.c. infusion over 60 min. of SK (250.000U). Reperfusion was assessed angiographically at 90 min. after the start of treatment. Blood samples were taken before and every 4 hours after dosing up to 24 hours. 74 patients were evaluable for this analysis. The results are:

	APSAC i.v.(n=36)		SK i.c.(n=37)	
Reperfusion	yes	no	yes	no
	23(63.9%)	13(36.1%)	25(67.6%)	12(32.4%)
time (hrs) from start of treatment				
CK peak	10.9	14.2	12.6	12.9
CK-MB peak	10.0	10.6	10.0	11.5
ASAT peak	12.8	15.0	13.7	15.4
peak value				
CK	1720.0**	2398.4**	2139.2	2964.7
CK-MB	164.2	208.0	164.3**	247.5**
ASAT	248.2	353.2	301.3	412.1
area under the curve (sq)				
CK	25453	33181	34023	40624
CK-MB	2216	2943	2431	3407
ASAT	3706	4926	4491	6200

Conclusion: a statistically significant difference ($p < .05$)** between the reperfused and non reperfused patients could only be demonstrated for the peak value of CK in the APSAC group and of CK-MB in the SK group.

* On behalf of the Dutch Invasive Reperfusion Study Group.