A COMPARISON BETWEEN FIBRINOLYSIS OF FRESH AND AGED CLOTS OR THROMBI BY rt-PA IN VIVO, EX VIVO AND IN VITRO J. Paulson, W. Hassmann, T.H. Müller, W.G. Eisele, Department of Biological Research, Dr. Karl Thomae GmbH, 7950 Biberach, Federal Republic of Germany

In view of the therapeutic applications of rt-PA it is of interest to investigate whether there is any difference in the lysisability of fresh and aged fibrin. The efficiency of fibrinolysis by rt-PA was studied in three different ways: In vivo, by measuring the thrombus weight of fresh (1 h) or aged (24 h) thrombi, with the clot location in the carotid artery of rabbits which had been treated with rt-PA (0.4 mg/kg) or saline for 1 h. In vitro, by measuring 125I-release of in vivo fresh (1 h) or aged (24 h) thrombi (labelled with ¹¹¹In, fibrinogen) suspended in vitro in plasma containing rt-PA (1 µg/ml), the thrombi were formed in the jugular vein and in the carotid artery of each rabbit. In vitro, by measuring 125I-release of fresh (1 h) or aged (6 or 24 h) human native whole blood clots, PPP-clots, PRP-clots and squeezed PPP-clots which were formed and lysed in vitro with rt-PA (1 µg/ml) as well as ex vivo with rt-PA lysed fresh (1 h) thrombi which showed better than aged (24 h) thrombi. This difference was more pronounced immediately after the onset of fibrinolysis, but decreased with time. However, in vitro relatively little difference was observed in fibrinolysis efficiency between fresh (1 h) and aged (24 h) thrombi, fibrinolysis of these clots was decreased (PPP > whole blood > PRP) with increasing clot retraction, which was almost complete within 1 h. This result was supported by confirmed that PPP-clots were "extracted," squeezing them just before lysis. Therefore we concluded that there is a considerably difference in lysis efficiency between fresh and aged thrombi which are observed in vivo and in vitro.

PLATELET INHIBITION (1)

THE THIENOPYRIDINE PCI 4099 INHIBITS THE ADP AGGREGATION PATHWAY OF HUMAN PLATELETS BY INTERFERING WITH THE BINDING OF FIBRINOMEN TO THE GLUCOPOPHIERIN IIb-IIIa COMPLEX C. Gonzalez (1), A. Stilril (1), C. Bouloux (2), J.-P. Cazenave (3), J.-P. Heptinstall (1), INSEM U 139, Centre de Transfusion Sanguline, Strasbourg, France (1) and Sanofi Recherche, Toulouse, France (2).

The thienopyridine, PCI 4099, is a synthetic structural analog of ticlopidine. After oral administration in man, it prolongs the bleeding time (PT) and inhibits ADP-induced aggregation. The purpose of the study was to evaluate the effects of oral administration of 200 mg per day PCI 4099 to 10 human volunteers for 7 days on primary hemostasis as assessed by bleeding time (bleeding time), platelet aggregation, and cAMP content in platelets and aggregation as a function of inhibition of the drug on the ADP-fibrinogen-GPIIb-IIIa pathway of aggregation. BT (measured by a Simplate device) was 4-8 min before treatment and 30 min after 7 days of treatment. Platelets were washed and reconstituted in Tyrode's buffer containing apyrase and hemostasis and to study the mechanism of inhibition of the drug on bleeding time (BT) and inhibits aggregation induced by ADP.

INTERACTIONS BETWEEN PGl2 AND INHIBITORS OF PLATELET AGGREGATION THAT ACT THROUGH CAMP S.J. Gray and S. Heptinstall, Department of Medicine, University Hospital, Nottingham, NG7 2UH, UK.

PGl2, has a biphasic effect on platelet aggregation with low concentrations of the prostaglandin potentiating aggregation and high concentrations inhibiting it. In this investigation we have studied the interaction of PGl2, with agents that inhibit platelet aggregation through an effect on CAMP. The agents concentrate on those that inhibit platelet aggregation, potentiating aggregation and inhibiting platelet aggregation. The potentiation of platelet aggregation by PGl2, was reduced by agents that inhibit platelet aggregation by interfering with the binding of fibrinogen to the GPIIb-IIIa complex on platelets.

MYELOPROLIFERATIVE DISEASE CHARACTERIZED BY THROMBOSIS, BLEEDING AND PLATELET DYSFUNCTION IN VIVO I.INJECTED WITH THE POLYMORPHIC LEUKEMIA VIRUS (PyLV). C. Sieling(1), A. Fusco(2), C. Portilla(3), A. Terteling(1), G. Tjada(1), G. Russo(1) and P.L. Mattioli, Dept of Experimental Medicine and Anatomy, University of Reggio Calabria at Catanzaro(1); Cur Dept of Experimental Endocrinology and Oncology(2) and Dept of Molecular and Cellular Biology and Pathology, Naples University(3), Italy.

After i.p. injection of PyLV, NIH/CLAC mice showed thrombosis in tail veins, ears, muscles and mesentery in addition to thrombosis and hematomas of subcutaneous tissues. This was followed by infarctions of lungs, heart and brain, that caused death of the animals. Laboratory evaluations of the infected mice showed normochromic anemia, mild thrombocytopenia and marked defects in the aggregation and in the secretion of ATP from platelets exposed to ADP, collagen, thrombin or A23187. About 10% of cells present in the bone marrow was formed by blast; 20% by multinucleated cells identified as megakaryocytes (') by peroxidase and acetylcholinesterase staining. The lesion was characterized by a marked lymphoid and megakaryocytic hyperplasia.

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