BRINOLASE DOSE PREDICTION WITH THE PROTEASE RESISTANCE TEST. W.H.E. Roschlau and D.M.C. Sutton, Department of Pharmacology and Toronto Western Hospital, University of Toronto, Toronto, Canada.

Systemic thrombolytic therapy with brinolase (fibrinolytic enzyme from *Aspergillus oryzae*) requires the determination of circulating inhibitors, a reliable method of predicting individual dosage to reduce inhibitors to predetermined targets, and post-treatment inhibitor determination to indicate adequacy of treatment. Several methods using chromogenic substrates were employed clinically with varying success, all allowing the calculation of approximate individual dosage.

The protease resistance test, a rapid method of total inhibitor determination in whole blood, is performed in a serial set of serological tubes containing fixed amounts of thrombin and in-

crements of brinolase, to which 1 ml of the patient's blood is added and incubated for 10 min at 37°C. The endpoint is determined visually as the tube in which lysis indicates a balance between the content of brinolase and the blood inhibitor titer, expressed as test-tube requirement (TTR) units. In 19 dose predictions in patients undergoing brinolase therapy the inhibitor reductions corresponded roughly to the amounts of enzyme infused, with greatest variability at higher doses; but the method provided a satisfactory guide to avoid overdosage in individual patients. The correlation ($r=0.896$) was better than that of other clinically applied methods, although patho-physiological conditions such as individual inhibitor composition, extra-vascular enzyme distribution and inhibitor binding may in part be responsible for the observed variability of results with all methods.

THE RELATIONSHIP BETWEEN REGULATION OF PROSTAGLANDIN METABOLISM AND PLATELET AGGREGATION.

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Platelet aggregation is mediated by prostaglandin (PG) endoperoxide and cAMP. But exogenous PGs might modify platelet function and might play a major role on the PG metabolism in platelet as well as endogenous PGs do. We studied the relationship between quantitative and qualitative regulation of PGs and cAMP and platelet aggregation, by incubation method adding exogenous PGs (PGE₁, etc) and antiaggregating agents such as heparin, dextran sulfate, carbocromen, α -tocopherol, per se in human platelet suspension. Platelet aggregation was studied photometrically adding thrombin. PGE₁, E₂, F₁ α and F₂ α were assayed by radioimmunoassay (RIA). cAMP was assayed by RIA. PG formation after incubation with the agents in platelet suspension was as follows; 1) PGF system was stimulated by PGE₁ and PGE₂. 2) PGE system was depressed by PGF₂ α . 3) PGF system was depressed by PGA₁. 4) PGE₁ stimulated cAMP and PGF system. 5) Aspirin, heparin, dextran sulfate and carbocromen had dose dependent inhibitory effect on thrombin induced platelet aggregation and had reducing effect on formation before adding thrombin. 6) Prenylamine and CDP-choline had inhibitory effect in vitro on platelet aggregation at higher concentrations than that of clinical use. CDP-choline reduced PGE levels but did not influence PGF levels. Prenylamine reduced PGF levels and stimulated cAMP formation at higher concentrations. 7) Dipyridamole and α -tocopherol did not reduce PG levels. This approach provided the results that platelet function was regulated by PG metabolism which is modified by exogenous PGs or some drugs. Antiaggregating agents can be classified by the quantitative and qualitative difference of PG formation.

FORMATION OF PROSTAGLANDIN CYCLO-PEROXIDES AND PROSTAGLANDINS BY PHOSPHOLIPASE A₂ IN PLATELETS OF NORMAL AND ESSENTIAL FATTY ACID DEFICIENT RATS. J.E. Vincent and F.J. Zijlstra. Department of Pharmacology, Medical Faculty, Erasmus University Rotterdam, P.O.Box 1738, Rotterdam, The Netherlands.

Phospholipase A₂ has a biphasic action upon rat platelet aggregation, enhancing after shorter and inhibiting after longer incubation periods. The first effect is inhibited by indomethacin.

Cycloperoxides and thromboxane-like substances and prostaglandins are formed on incubation with the enzyme in the same amounts whether aggregation is induced or not. Formation of cycloperoxides and thromboxanes is not leading to aggregation. Phospholipase A₂ enhances the aggregation of the platelets of essential fatty acid deficient rats. Only very small amounts of cycloperoxides and thromboxane-like substances are formed. It is concluded that cycloperoxides and thromboxanes can enhance, but not induce aggregation in rat platelets.