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 (fibrinolysic 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 dilution of sera containing fixed amounts of enzyme-infused, 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, extravascular 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 PGE might modify platelet function and might play a major role in the PG metabolism in platelet as well as in platelet-PGs do. We studied the relationship between quantitative and qualitative regulation of PGEs and cAMP and platelet aggregation, by incubation with exogenous PGEs (PGE1 etc.) and anti-aggregating agents such as heparin, dextran sulfate, carboxybenzyl-α-tocopherol, and so on in human platelet suspension. Platelet aggregation was studied spectrophotometrically adding thrombin. PGE1, PGE2, PGF and PGI2 were assayed by RIA. In aggregation induced by thrombin, PGs formation after incubation with the agents in platelet suspension was as follows: 1) PGE2 system was stimulated by PGE1 and PGE2. 2) PGE2 system was depressed by PGE1. 3) PGE1 system was depressed by PGF2. 4) PGE1 stimulated cAMP and PGI2 system. 5) Heparin, dextran sulfate and carboxybenzyl-α-tocopherol had dose dependent inhibitory effect on thrombin induced platelet aggregation and had reducing effect on formation before adding thrombin. 6) PGE1 and PGI2 had inhibitory effect in vitro on platelet aggregation at higher concentrations than that of clinical use. PGF2 reduced PGE levels but did not influence cAMP levels. PGI2 reduced PGE levels and stimulated cAMP formation at higher concentrations. 7) PGI2 and PGI2 reduced PGI2 induced platelet aggregation at higher concentrations. 8) PGE1 and PGI2 reduced PGI2 induced platelet aggregation at higher concentrations. 9) PGI2 reduced PGE levels and stimulated cAMP formation at higher concentrations. 10) PGI2 reduced PGE levels and stimulated cAMP formation at higher concentrations. 11) PGI2 reduced PGE levels and stimulated cAMP formation at higher concentrations. 12) PGI2 reduced PGE levels and stimulated cAMP formation at higher concentrations. 13) PGI2 reduced PGE levels and stimulated cAMP formation at higher concentrations. 14) PGI2 reduced PGE levels and stimulated cAMP formation at higher concentrations. 15) PGI2 reduced PGE levels and stimulated cAMP formation at higher concentrations. 16) PGI2 reduced PGE levels and stimulated cAMP formation at higher concentrations. 17) PGI2 reduced PGE levels and stimulated cAMP formation at higher concentrations. 18) PGI2 reduced PGE levels and stimulated cAMP formation at higher concentrations. 19) PGI2 reduced PGE levels and stimulated cAMP formation at higher concentrations. 20) PGI2 reduced PGE levels and stimulated cAMP formation at higher concentrations. 21) PGI2 reduced PGE levels and stimulated cAMP formation at higher concentrations. 22) PGI2 reduced PGE levels and stimulated cAMP formation at higher concentrations.