

A STUDY OF THE MECHANISMS INVOLVED IN COLLAGEN-INDUCED INTRAVASCULAR PLATELET AGGREGATION. G.M. Smith and G. Mallarkey. School of Pharmacy, Robert Gordon's Institute of Technology, Aberdeen, Scotland.

Intravascular platelet aggregation can be monitored by measuring the fall in the number of circulating platelets after the injection of an aggregating agent. The Technicon Auto-counter was modified to count platelets continuously. Rats were anaesthetised and the trachea and jugular vein were cannulated. A double cannula was inserted into a carotid artery.

Collagen gave consistent and dose-dependent falls in platelet count. Infusion of trisodium citrate gave a dose-dependent inhibition of collagen-induced aggregation with 2 mg/kg/min producing 100% inhibition. Indomethacin 1-8 mg/kg and aspirin 10-160 mg/kg produced up to 60% inhibition of collagen-induced aggregation giving a biphasic dose-response curve. Sulphinpyrazone 20-160 mg/kg and piroxicam 1-8 mg/kg gave dose-dependent inhibitions of aggregation. None of the cyclo-oxygenase inhibitors studied or sulphinpyrazone completely inhibited collagen-induced aggregation. Attempts to produce 100% inhibition by infusing adenosine or low doses of citrate with indomethacin were unsuccessful. High doses of collagen were more resistant to cyclo-oxygenase inhibitors than low doses of collagen.

This study has shown that trisodium citrate will completely inhibit collagen-induced aggregation and that both high and low doses of collagen produce aggregation in the rat that is partially mediated by products of arachidonic acid metabolism. The biphasic nature of the dose-response curves obtained with indomethacin and aspirin suggests that the higher doses are inhibiting the cyclo-oxygenase in the walls of blood vessels as well as in platelets thus reducing the endogenous release of prostacyclin. The nature of the arachidonic acid-independent pathway has yet to be demonstrated.

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PRIMARY PLASMA THERAPY FOR THROMBOTIC THROMBOCYTOPENIC PURPURA. D.C. Case, Jr. Division of Hematology, Department of Medicine, Maine Medical Center, Portland, Maine, 04102.

A 25-year old male was admitted for an episode of right sided headache and subsequent generalized seizure. On admission his temperature was 37.6°. He had generalized petechiae and conjunctival hemorrhages. Organomegaly and lymphadenopathy were absent. There was mild left sided weakness. The Hgb. was 6.9 g/dl., reticulocyte count 10%, WBC 11,500/mm³, and platelet count 10,000/mm³. There were numerous schistocytes on the peripheral smear; bone marrow revealed pancytopenia. Coagulation studies were normal. The BUN was 30, and the creatinine 1.7 mg/dl. Plasma was positive for Hgb. CT scan was negative for gross intracranial bleeding. The diagnosis of T.T.P. was made. On admission, the patient received 10 units of platelets and 2 units of packed red blood cells. He did not require further red cell or platelet transfusions during the rest of his hospital course. He was then started on infusions of fresh-frozen plasma. He then received one unit every 3 hours for 6 days, one unit every 6 hours for 2 days, then one unit every 12 hours for 2 days and finally 1 unit daily for 5 days. The response was immediate. After the infusions were started, the hematologic parameters steadily improved. The patient's hematuria rapidly improved. Further CNS symptoms did not appear. The patient's Hgb. was 12 g/dl, and reticulocyte count was 2.5% by the 9th day. His platelet count was normal by the 4th day. The patient was discharged on the 15th day. Infusions of plasma were discontinued at the time of discharge. The patient required plasma therapy 4 weeks later for recurrent thrombocytopenia (50,000/mm³). The patient has remained normal for 9 months since therapy and further plasma has not been required. Primary plasma therapy for T.T.P. as sole treatment should be further studied.

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MALONDIALDEHYDE FORMATION INDUCED BY DIFFERENT COLLAGENS. L. Balleisen and J. Rauterberg. Department of Medicine and Institute for Arteriosclerosis Research, University of Münster, W. Germany.

To get close information about the characteristics of collagen induced MDA formation, platelet aggregation was induced by collagen type I, III a. V in dissolved and fibrillar form and by methylated type I collagen. The MDA formation was measured in the course of aggregation. In case of Meth.c. MDA production is induced also if under certain incubation conditions no aggregation is detectable.

During the pl.aggr. induced by dissolved c. some MDA production was seen before the slope of the aggregation curve increased. Parallel to the increasing slope MDA increased fast, and some further increase over a 30 min. period was observed. For fibrillar and meth.c. MDA formation begins just with the increasing slope and reaches a stable plateau. In case of meth.c. the plateau is reached immediately after the maximum of aggregation occurred, in that of fibrillar c. some min. after maximal aggregation. For meth.c. the results obtained in the incubation system were comparable to that in the aggregation system.

For meth.c. the kinetics of MDA formation in both systems were further defined. In both systems a concentration dependent saturation kinetic was obtained. In the aggregation system the concentration dependent increase of MDA formation was somewhat faster as in the incubation system and reached its saturation level at a lower collagen concentration.

From the increasing and long lasting MDA formation induced by the interstitial collagens we might speculate that in vivo the stimulating activity of the collagens may work for a long time in conditions where the prostacyclin production of the vessel wall is decreased. The characteristics of MDA formation induced by meth.c. suggest that this c. may be a good tool for in vitro studies.

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NORMAL PROSTACYCLIN-LIKE ACTIVITY IN A PATIENT WITH THROMBOTIC THROMBOCYTOPENIC PURPURA. M. Pini, C. Manotti, R. Quintavalla and A.G. Dettori. 5th Medical Division and Centre for Haemostatic Diseases, Ospedali Riuniti, Parma, Italy.

Deficiency of prostacyclin (PGI₂) has been related to the pathogenesis of thrombotic thrombocytopenic purpura (TTP), and reduced PGI₂ activity is thought to be secondary to a lack of plasma factor(s) which normally stimulates PGI₂ production. We measured PGI₂ production by means of the method of Moncada et al (Lancet 1:18, 1977), as platelet aggregation inhibitory activity released by venous specimen removed surgically in a 52 year-old woman with TTP in the acute phase of the disease. The patient was subsequently cured by plasma exchange.

Platelet aggregation inhibitory activity released from venous tissues of the patient was normally detectable and comparable to that of a healthy control. Moreover, patient plasma was able to induce release of prostacyclin-like activity from exhausted veins (both from patient and normal control) as well as normal plasma. Hence release of PGI₂-like activity from venous tissues and ability of plasma to stimulate prostacyclin synthesis in normal vascular tissues were not impaired in our patient with TTP in the acute phase of the disease.

Our findings demonstrate that PGI₂ deficiency is not implicated in the pathogenesis of all cases of TTP.