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RIBAVIRIN: STUDIES OF THE EFFECTS OF THE ANTIVIRAL DRUG ON PLATELET FUNCTION. T.M. Cosgriff (1), P.G. Canonico (1), L. Hodgson (1), D. Parrish (1), T. Chapman (1), J.W. Huggins (1), Z.-J. Gong (2), L.-B. Xiang (2), and C.-H. Hsiang (2). United States Army Medical Research Institute of Infectious Diseases, Ft. Detrick, Frederick, MD 21701-5011, U.S.A. (1), and Hubei Medical College, Wuhan, Hubei, Peoples Republic of China (2).

Ribavirin is a broad-spectrum antiviral drug which is presently undergoing testing in patients with AIDS-related complex. It has also been shown to have activity against respiratory syncytial virus, Sicilian sandfly fever virus, influenza A and B viruses, as well as several hemorrhagic fever viruses. It has proved effective in clinical trials in Lassa fever and shows promise as therapy for hemorrhagic fever with renal syndrome. Because platelet dysfunction may contribute significantly to hemostatic impairment in viral hemorrhagic fever, the effects of ribavirin on platelet function were measured in rhesus monkeys after daily injections of 100 mg/kg IM for 14 days. Drug administration led to a significant increase in platelet count associated with megakaryocyte hyperplasia but had no effect on aggregation of platelet-rich plasma (PRP) in response to either collagen (1.6 µg/ml) or ADP (10 µM/ml). Aggregation in whole blood was also unaffected. Addition of ribavirin to human PRP in concentrations up to 0.5 mg/ml had no effect on aggregation in response to collagen, ADP, or epinephrine (5 µg/ml). Preliminary data from Chinese patients treated with ribavirin for hemorrhagic fever with renal syndrome also reveal no evidence of drug-induced platelet dysfunction as indicated by normal aggregation and release reactions to collagen (3 µg/ml) and ADP (10 µM/ml). Bone marrow studies of megakaryocyte number and ploidy are presently underway to further characterize drug-associated thrombocytosis.

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MECHANISMS OF PLATELET AGGREGATION BY ACIDIC MUCOPOLYSACCHARIDE EXTRACTED FROM STICHOPUS JAPONICUS SELENKA IN HUMANS AND RABBITS. J. Z. Li and E. C.-Y. Lian. Institute of Hematology, Tianjin, China and the Center for Blood Disease, University of Miami and Veterans Administration Medical Center, Miami, FL, USA

It has been reported that acidic mucopolysaccharide extracted from sea cucumber (Stichopus japonicus selenka) (SJAMP) induced the aggregation of human and animal platelets by an unknown mechanism. Using platelet-rich plasma (PRP) and washed human and rabbit platelets we studied the effects of storage, platelet inhibitors, and various plasmas and their fractions on SJAMP-induced platelet aggregation. We found that the lowest concentrations of SJAMP required for aggregation of human and rabbit platelets were 0.4 and 2 ug/ml respectively. The reactivity of human platelets to SJAMP decreased with time after drawing of blood; rabbit platelets did not show this phenomenon. Platelet inhibitors such as aspirin, indomethacin, apyrase, antimycin, 2-deoxy-D-glucose, and EDTA inhibited by 50 to 100% the aggregation of human platelets induced by SJAMP; but these inhibitors had no effect on SJAMP-induced aggregation of rabbit platelets. Washed human and rabbit platelets were not aggregated by SJAMP. The aggregation of washed human platelets by SJAMP was restored completely by human or rabbit plasma, by human fibrinogen, or by 0 to 30% saturated ammonium sulfate fraction but not by serum. The aggregation of rabbit platelets by SJAMP could only be restored by rabbit plasma or serum, or by 50 to 60% saturated ammonium sulfate fraction. The data indicate that the mechanisms of aggregation of human and rabbit platelets by SJAMP are different. THe SJAMP-induced human platelet aggregation is dependent upon metabolism, release of ADP and the cyclooxygenase pathway requiring fibrinogen and Ca^{++}. The aggregation of rabbit platelets induced by SJAMP is independent of metabolism, release of ADP and cyclooxygenase pathway, and does not require fibrinogen and Ca^{++}, but needs certain protein(s) in the 50 to 60% saturated ammonium sulfate fraction of rabbit plasma.

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REFRACTORINESS OF PLATELETS AFTER REVERSIBLE STIMULATION BY ADP, PAF AND AA. R. Voss, H.D. Ohanes, H. Ditter, F.R. Matthias. Dept. of Internal Medicine, Giessen, F.R.G.

It has been observed that platelets which have been stimulated by thrombin, ADP or platelet-activating factor(PAF) show an inhibited response to a subsequent stimulation by the same agonist. We performed a cross-over stimulation of human platelets (PRP) with the four agonists ADP, PAF, arachidonic acid(AA) and collagen (COL); after a first stimulation with a dose giving a reversible aggregation (0,1-0,4x10^{-6}M ADP, 0,1-0,5x10^{-8} M PAF) or a shape change (0,05-0,1mM AA, 0,4 ug/ml COL) the platelets were again stimulated after 5 min with the same or a higher dose, usually resulting in an irreversible aggregation (1,0-3,0x10^{-6}M ADP, 1,0-5,0x10^{-8} M PAF, 0,3-0,5mM AA, 1,0 ug/ml COL).
ADP-, PAF- and AA-stimulation were inhibited by a prestimulation with the same agonist (ADP/ADP 60% inhibition, PAF/PAF 100% inhibition, AA/AA 10% inhibition); ADP and PAF did not or only slightly inhibit each other. Prestimulation with AA changed a reversible ADP- or PAF-induced aggregation into an irreversible one, and a reversible AA-stimulation was increased to irreversible by ADP-prestimulation. COL-aggregation was not influenced by any prestimulation nor did a COL-prestimulation influence the second stimulation by any of the four agonists.
The refractoriness of platelets for ADP and PAF after prestimulation with the same agonist may be explained by receptor internalization; in the case of ADP the effect lasted for at least one hour. The enhancement of ADP- and PAF-aggregation by an AA-prestimulation can be explained by other investigations which have shown that the arachidonic acid pathway acts as a positive feedback mechanism in platelets.

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TRANSITORY INFLUENCE OF FIBRINOGEN/FIBRIN DEGRADATION PRODUCTS (FDPs) ON PLATELET AGGREGATION. S.D. Nelson, A.J. Moriarty, R. Hughes and K. Balnave.
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This paper describes a pilot study to investigate the influence of FDPs on platelet aggregation in a small cohort of patients (N = 12) undergoing systemic thrombolytic therapy with streptokinase (600,000 I.U. or 1,500,000 I.U. delivered over 30 minutes) for acute myocardial infarction.

Serial pre- and post-therapy blood samples were anticoagulated with sodium citrate, and whole blood aggregation studies carried out over 24 hours using a Crono-log 540 aggregometer and the standard adenosine diphosphate (ADP), adrenalin (A), collagen (C) and ristocetin (R) aggregating agents.

Results, in the form of mean percentage voltage change from baseline voltage change, measured at 8 minutes after addition of aggregant, are presented for the cohort at times in Figure 1. Serial aggregometry tracings for one representative patient are shown in Figure 2.

Clearly comparison of the 1 hour and 18 hour results for each aggregating agent shows a variable but consistent return towards baseline (at FDP < 8 µg/ml) as the FDP concentration drops. This implies that, provided the same platelet population is involved, there is no generalised permanent platelet defect consequent on systemic STK therapy. Coulter counter measurements do not indicate the increase in platelet number that would suggest a large influx of new platelets.

Aggreg. Agent	Mean % voltage change from baseline At t=1hr	At t=18 hr
ADP	-73	-32
A	-50	+2
C	-27	-15
R	-72	-61
Mean FDP Conc.	576	133

Figure 1

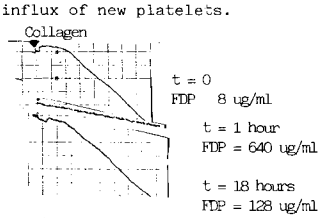

Figure 2