2016

DN.9693 COMPARED WITH PROSTACYCLIN AND PROSTAGLANDIN E_1 IN SEVEN PLATELET TESTS. J.R. O'Brien, M.D. Etherington and G.P. Salmon. Central Laboratory, St. Mary's Hospital, Portsmouth PO3 6AG, Hampshire, England.

A new drug, DN.9693, has low Km phosphodiesterase inhibitory properties. Its effect on seven broad spectrum platelet "function" tests has been compared with the effects of prostacyclin (PGI_2) and prostaglandin E_1 (PGE_1). The tests were (1) platelet aggregation induced by ADP, collagen, adrenaline, thrombin, arachidonic acid and ristocetin; (2) a new test in which platelets aggregate after adding distilled water to cause osmotic stress; (3) the loss of platelets washed in buffered saline; (4) clot retraction; (5) the glass bead column platelet retention test; (6) the in vitro filter "bleeding time" (see two other submitted abstracts); (7) the amount of platelet factor 4 (PF4) which "leaks" from platelets at room temperature. PGI_2 inhibited all seven tests, 50% inhibition of the various tests required from 0.1 to 44ng/ml of PGI_2. PGE_1 also inhibited in all tests but on average required 18 times higher concentrations. Thus an increase in cAMP may be relevant to all these tests, but an understanding of the mechanisms involved is incomplete. DN.9693 inhibited only the first four tests; the equi-active concentration was about 600 times that of PGI_2. DN.9693, 2.5µg/ml, caused 50% inhibition of ristocetin induced aggregation and at 4µg/ml had a minor effect on the filter bleeding time. Thus DN.9693 may affect the platelet membrane glycoproteins. In conclusion it is confirmed that PGE_1 is less active than PGI_2 but has similar activities. DN.9693 when studied in these tests has many, but not all, of the prostaglandin-like properties.

2017

EFFECT OF TRIFLUOPERAZINE (TFP) ON HUMAN PLATELET MEMBRANE. C.T. Wang (1), J.Y. Lee (1), J.C. Chen (2), Y.J. Shiao (1), W.J. Tsai (1). Institute of Life Science, National Tsing Hua University, Hsinchu (1) and Laboratory of Electron Microscopy, College of Science, National Taiwan University, Taipei (2), Taiwan, ROC (Formosa).

TFP is a lipophilic antipsychotic drug. The drug will first encounter with cell membrane when adding it into a cell suspension. The effect of TFP on plasma membrane of the gel-filtered human platelet was investigated by : 1) scanning electron microscopy (SEM); 2) measuring the leakiness of marker enzymes and compound; 3) estimating its solubility in membrane. The cells were suspended in the modified Tyrode's buffer containing 0.1% dextrose, 0.2% of bovine serum albumin and without calcium. The SEM study showed that platelet changed shape from disc to ellipsoid in 10 µM TFP. Increasing the TFP concentration from 20 µM to 50 µM resulted in changing the cell from ellipsoid to sphere with a wavy surface. The drug did not cause any significant change in the cell volume. TFP of 70 µM caused platelet becoming a round ball shape with a spongy-like cell surface. 100 µM TFP caused more than 90% of cells to lyse and to agglutinate with each other. The time course of morphological change of the TFP-affected platelets showed that the cells swelled into irregular shape within 2 min. Apparent leakiness of serotonin was observed at 20 µM TFP, while the leakages of both lactate dehydrogenase and acid hydrolase were found at 40 µM TFP. The TFP uptake study showed that platelet was permeable to TFP by simple diffusion. The partition coefficient of TFP in platelet membrane was estimated to be 1×10^4. These results indicate that TFP molecules are solubilized in membrane. The extent in perturbation of the membrane structure depends on concentration of the drug used. (This research was supported by a grant from the National Science Council of the Republic of China.)

2018

EVALUATION ON EFFECTIVENESS OF LOW DOSE ASPIRIN THERAPY FOR PROTECTION OF THROMBUS FORMATION. S.Kariyone, M.Hirakuri, T.Yui, and T.Uchida. Department of Internal Medicine, Fukushima Medical College, Fukushima, 960 Japan.

In order to protect thrombus formation, administration of low dose aspirin has become common. However, its significance for this purpose is still not clear. Effect of small dose of aspirin (ASA) on platelet aggregation and ability of malondialdehyde(MDA) formation in platelet by the addition of arachidonic acid in vitro were investigated. In clinical study, platelet aggregation, MDA formation of platelet, serum β-thromboglobulin(β-TG), platelet factor 4(PF4) and thromboxane B_2($TX-B_2$) levels were measured before and after low dose aspirin therapy.

Platelet aggregations by ADP, collagen, epinephrin and arachidonate as inducers were significantly suppressed under 12.5 ug/ml ASA in the medium. MDA formation of platelet was remarkably inhibited under 1.6 ug/ml of ASA in the medium in vitro.

In patients, single oral dose of 50 mg ASA showed no change on platelet aggregation while the ability of MDA formation decreased 50% of the before. Serum concentration of ASA after oral dose of 50 mg ASA only showed 1.5 to 6.0 ug/ml at maximum.

Daily dose of 50 mg ASA was continued during 10 days. Changes of various factors due to the time course were observed. Inhibitions of platelet aggregation were seen from 5th day on ADP and collagen and from 2nd day on epinephrin and arachidonate as inducers during the therapy. MDA formations of platelet were decreased quickly and it became almost zero at 5th day. ASA levels in the patient serum reached plateau as 8 or 9 ug/ml from 3rd day.

Various patients with a possibility of thrombus formation were administered daily 50 mg ASA during 10 days. Platelet aggregations and MDA production, serum β-TG, PF4 and TXB_2 levels were measured before and after the therapy. Platelet aggregations by ADP, collagen and epinephrin as inducers were significantly suppressed after the therapy and MDA production of platelet was also markedly decreased after the therapy. There were no significant changes in serum β-TG and PF4 levels while TXB_2 level tended to decrease after the therapy.

From these results, it was concluded that daily 50 mg ASA oral dose was certainly effective for protection of thrombus formation.

2019

STAI (Studio Ticlopidina Angina Instabile) PROJECT. TICLOPIDINE IN UNSTABLE ANGINA. F. Violi, C. Cimminiello, S. Chierichetti, M. Scatigna, P. Rizzon, F. Balsano. STAI Group - Rome - Italy.

The treatment of patients suffering from unstable angina (UA) with antiplatelet drugs is a therapeutic approach that provided interesting results.

Patients given aspirin, that inhibits cyclooxigenase pathway (CP) showed a significant reduction of cardiovascular events.

Quite surprisingly sulfinpirazone, that possesses a mechanism of action similar to aspirin, did not influence cardiovascular complications of UA patients.

To further investigate the role of platelets in UA patients, we planned to study if ticlopidine (T), that inhibits platelet function by blocking fibrinogen binding to platelets, influences the clinical course of UA.

The study will include 1200 randomised patients given conventional therapy with or without T (500 mg/daily).

Patients enrolled have to show one of the following clinical pictures:

1) angina at rest;
2) "crescendo angina";
3) new onset angina.

Clinical symptoms should be present within 30 days. The follow-up will last 6 months.

Primary end-point of the study is the incidence of fatal and non-fatal myocardial infarction and of vascular death.

Apart from the possible influence of T in the natural course of UA, the study will offer the opportunity to find and incidence pattern of UA cardiovascular complications in Italy.