

DIFFERING EFFECTS OF TICLOPIDINE AND TWO PROSTAGLANDIN SYNTHETASE INHIBITORS ON MAXIMUM RATE OF ADP-INDUCED AGGREGATION. J. J. Bruno, D. Yang and L.A. Taylor. Institute of Biological Sciences, Syntex Research, Palo Alto, CA, USA.

Many platelet inhibitors are known which block the secondary (2°) phase of ADP-induced aggregation. These agents normally inhibit platelet cyclooxygenase (CO). Agents which are able to inhibit primary (1°) ADP-induced aggregation usually cause elevation of platelet cAMP. Ticlopidine hydrochloride (T), a drug which does not stimulate platelet adenylate cyclase or inhibit platelet cAMP phosphodiesterase, or platelet CO, inhibits 1° ADP-induced aggregation. Healthy human volunteers were dosed orally from 3-8 days with doses of T from 125 to 500 mg/day. When the maximum rate of ADP-induced aggregation on the day following cessation of dosing was compared with that obtained predosing, statistically significant inhibition of maximum rate was obtained at each dose. Similar studies were done with naproxen (N) a CO inhibitor. Healthy human volunteers were given 125 to 1000 mg/day of N. When the rates of ADP-induced aggregation at 3 and 8 hours post-dosing were compared to predose rates, there were no statistically significant differences at any dose. At these times collagen and arachidonic acid-induced aggregation were essentially totally inhibited. An experimental agent, 5-benzoyl-1, 2-dihydro-3H-pyrrolo [1,2-a]-pyrrole-1-carboxylic acid, with potent platelet CO inhibiting activity, given orally to human volunteers at 2.5 to 200 mg/day showed the same results at 3 and 24 hours post dosing as did N.

We conclude that T is an inhibitor of 1° phase of ADP-induced aggregation, and that agents with CO-inhibiting action alone are incapable of inhibiting 1° phase of ADP-induced aggregation despite occasional reports to the contrary.

## 1308

CLINICAL AND PLATELET FUNCTION CHANGES BY SULFINPYRAZONE (S) IN ESSENTIAL MIXED CRYOGLOBULINEMIA (EMC). C. Boschetti, M. Cortellaro, F. Invernizzi, P. Massaro, A. Rigolone and E.E. Polli. Medical Clinic, University of Milan, Italy.

EMC represents a typical model of immune complexes (IC) disease. The interaction between platelets and IC through Fc receptors plays an important role in the pathogenesis of IC clinical features. The effects of 2 months' treatment with an antiaggregating drug, sulfinpyrazone (S) (400 mg twice a day) were investigated in 15 patients (9 male and 6 female, mean age 55 yr) with EMC (cryocrit 2-40%). All patients presented with the purpura arthralgia syndrome. In 2 cases there was evidence of renal impairment (proteinuria < 1.5 g/day). Duration of EMC was 2-8 yr. The following platelet function tests were carried out on 12 patients before and after S treatment: platelet production time (PPT), CPA ratio and plasma  $\beta$ -TG. Basal data of platelet function: 4/12 patients had PPT < 6.5 days (normal value  $9.88 \pm 0.19$ ), 4/12 had a CPA ratio of < 0.8, and 10/12 had  $\beta$ -TG of  $\geq 60$  ng/ml (n.v.  $35.11 \pm 13.93$ ). Seven patients showed a clinical improvement. These patients had a shorter basal PPT and lower CPA ratio than the others, and after treatment PPT was markedly lengthened ( $8.75 \rightarrow 12.46$  days) and the CPA ratio increased ( $0.774 \rightarrow 0.995$ ); in the other patients who showed no clinical improvement PPT and the CPA ratio remained almost unchanged ( $9.06 \rightarrow 9.09$  and  $0.94 \rightarrow 0.89$  respectively). Plasma  $\beta$ -TG levels were practically unvaried in both groups.

These data indicate that treatment with S may be useful in IC diseases, particularly in subjects in whom laboratory tests evidence accelerated platelet consumption *in vivo*.

## 1307

STUDY OF A MEMBRANE PHYSICO-CHEMICAL MECHANISM OF THE PLATELET ANTI-AGGREGATING EFFECT OF TICLOPIDIN. J.F. Stoltz, C. Solagna, A. Nicolas and M. Verry. Groupe d'hémorhéologie, Centre de Transfusion Sanguine, Nancy - et Laboratoire Millot Sanofi, Paris - France.

In view of earlier investigations which had revealed that Ticlopidin interferes with fatty acids, the authors decided to study the adsorption and penetration of the molecule on the platelet membrane, as well as its influence on the "membrane microviscosity" of the platelet membrane.

The study was carried out using two different techniques: - study of the adsorption-penetration and/or desorption kinetic by means of a molecule labeled  $^{14}C$  - study of membrane microviscosity by fluorescence polarization measurement (anisotropy of light emission) after incorporating a fluorescent molecule (1.6 diphenyl-1,3,5 hexatriene - DHP).

The measurements were carried out on normal platelet suspensions in a physiological salt medium ( $I = 0.145$  M).

The results reveal: - very rapid fixation of the molecule, whatever the quantities involved (< 10 mins) - absence of saturation of the adsorption sites, even at very high concentrations (> 400  $\mu$ g/ml). - a very low reversibility of the fixation bond (approx. 25 %) estimated by elution and by elution competition. - a decrease (15 %) in membrane microviscosity for concentrations superior to 200  $\mu$ g/ml (membrane microviscosity usually increases during platelet activation due to aggregating agents).

On the basis of these results the authors suggest that a physico-chemical mechanism of adsorption-penetration both in an on the platelet membrane might explain some of the biochemical and pharmacological effects observed.

## 1309

PLATELET SURVIVAL IN RABBITS TREATED WITH UK37248 OR WITH SULPHINPYRAZONE. J.A. Davies and V.C. Menys. University Department of Medicine, The General Infirmary, Leeds LS1 3EX, U.K.

Survival time of  $Na^{51}Cr$ -labelled platelets was measured in rabbits and results calculated by linear regression. In 10 normal rabbits, survival was  $81.9 \pm 3.3$  hours (mean  $\pm$  SEM). This was not significantly different at  $85.2 \pm 4.6$  hours in 8 rabbits in which survival was repeated following trauma to the aorta by single passage of an inflated balloon catheter. Indwelling nylon cannulae (4FG) were inserted through the femoral artery to lie the full-length of the aorta. Platelet survival was significantly ( $p < 0.01$ ) shortened from  $79.7 \pm 3.7$  hours in 9 sham-operated animals to  $62.2 \pm 2.4$  hours in 10 cannulated rabbits. Administration of the thromboxane synthetase inhibitor UK37248 at 10mg/kg in two oral doses daily did not prolong platelet survival ( $64.5 \pm 3.4$  hours,  $n = 14$ ). Measurement of serum  $TxB_2$  concentration in samples taken at random indicated inhibition ranging from 10 to 95% during the five days of study. Incomplete inhibition of thromboxane synthetase might account for the lack of effect. However treatment of 4 cannulated rabbits with sulphinpyrazone 20mg/kg/day also failed to prolong platelet survival ( $53.9 \pm 3.0$  hours). The results suggest that this model of platelet survival may prove resistant to the effects of anti-platelet drugs.