FREE COMMUNICATIONS VI

Platelets: Inhibitor Drugs

MECHANISM OF ACTION OF HALOFENATE, A PLATELET INHIBITOR. G.R. Favis and R.W. Colman, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, U.S.A.

Halofenate (Hal) has previously been shown to inhibit epinephrine (Epi) and ADP induced platelet aggregation and 14 C-serotonin release. We further investigated the site of action of Hal by examining platelet shape change as a membrane event and malondialdehyde (MDA) formation as a measure of prostaglandin synthesis. Platelet-rich-plasma (PRP) with and without Hal was diluted in an EDTA buffer and examined in a spectrophotometer modified for stirring and maintained at 37°. ADP induced increase in absorbance was recorded and the velocity of the shape change curve was plotted against ADP concentration. MDA production was measured by the thiobarbituric acid assay and utilized a DEAE-52 cellulose column to concentrate the chromogen. Hal in pharmacologic concentrations (.96mM) had no effect on Epi induced primary aggregation or on ADP induced shape change. However, at higher than pharmacologic amounts (3.36mM), Hal did inhibit ADP induced shape change. Epi-induced MDA formation (.18 μ M-.33 μ M) normally occurs concomitant with the second phase of aggregation and serotonin release but was markedly decreased by Hal (.06 μ M-.085 μ M). This inhibition was not due to a direct effect on prostaglandin synthesis since sodium arachidonate (1mM) caused secondary aggregation in PRP treated with Hal but not PRP treated with aspirin (4mM). Hal (.96mM) does not seem to inhibit platelet aggregation through an inhibition of ADP induced shape change or of Epi induced primary aggregation. Since Hal treated platelets respond to arachidonate, Hal must work at some earlier step than arachidonate induced prostaglandin synthesis. We suggest that this may be an alteration of the platelet membrane structure which makes ADP and Epi binding sites less accessible or which impairs arachidonic acid release by phospholipase. Decreased MDA formation and inhibition of aggregation would then be secondary to this membrane change.

PHARMACOLOGICAL EVALUATION OF TICLOPIDINE, A NOVEL INHIBITOR OF PLATELET FUNCTION. M. Johnson, P.L. Walton, R.C. Cotton and *C.J.L. Strachan. Imperial Chemical Industries Ltd., Macclesfield, Cheshire, England, and *Queen Elizabeth Hospital, Birmingham, England.

Ticlopidine (T), 5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno(3,2-C)pyridine hydrochloride (a product of Parcor Research) has been evaluated as an antiplatelet agent in various animal species and in human volunteers. T was inactive in vitro, but inhibited platelet aggregation induced by ADP, collagen, thrombin, arachidonic acid and prostaglandin (PG) endoperoxide, when administered orally to mice, rats, rabbits, guinea pigs, pigs, dogs and baboons. Platelet adhesiveness was reduced but platelet survival time was normal in treated animals. Basal PG synthesis and platelet ultra-structure were unaffected by T. T protected against acute thrombocytopenia and death from pulmonary embolism induced by i.v. injection of ADP or collagen. Thrombus formation in experimental models of extra-corporeal circulation and deep venous thrombosis was also impaired.

In man, a single oral dose of 500mg was shown to be a potent inhibitor of ADP, collagen, adrenaline, ristocetin, bovine fibrinogen and 5HT-induced aggregation. A dose-effect relationship was apparent, 250 and 500mg resulting in ~47 and 75% inhibition of ADP-induced aggregation respectively. Inhibition was sustained by chronic daily dosing.

There was a delay in the onset of action of T in vivo, but which then persisted after withdrawal for at least 48 hours, with no evidence of rebound hyperactivity. The duration of action of T correlated with platelet survival time, suggesting an irreversible modification of platelet function. T is a potent platelet inhibitor, exhibiting a novel mode of action and lack of agonist specificity, which may be of value in the treatment of thrombotic conditions.