

IN VIVO STUDIES WITH A NEW ANTIAGGREGATING DRUG EMD 26644, A MERCAPTO-OXAZOLYL-CARBON-ACID DERIVATIVE. H.J.Krzywanek, U.Pietsch and K.Breiddin. Department of Angiology, Medical Center, University Frankfurt a.M., Germany.

The inhibitory effect of EMD 26644 on platelet function has been studied with the following methods: spontaneous aggregation (PAT III), ADP-, collagen-

induced aggregation, primary shape change of thrombocytes at 37°C incubation temperature and platelet spreading. Duke's bleeding time, platelet count and some coagulation parameters like partial thromboplastin time, Quick's test, fibrinogen, thrombin time and factor VIII-assay as well as platelet spreading were unchanged throughout the test period.

An aspirin like inhibitory effect on platelet aggregation and primary shape change was observed 48 - 72 hrs. after the ingestion of a single dose of 250 mg EMD, which lasted for 2 - 3 weeks. A prolonged antiaggregating effect was achieved by the continuous oral administration of 25 - 50 mg EMD for a period of 2 - 3 months. No potentiation of the antiaggregating effect was seen, if ASA was given in addition to EMD 26644.

In comparison with aspirin the new compound seems to have some advantages: the same antiplatelet properties are achieved with a much lower dose and no side effects have been reported so far. Clinical studies will have to confirm whether EMD 26644 is an effective antithrombotic agent.

ANTITHROMBOTIC ACTIVITY OF A POTENT, NEW AGENT, 6,7-DICHLORO-1,2,3,5-TETRAHYDROIMIDAZO[2,1-b]QUINAZOLIN-2-ONE HYDROCHLORIDE MONOHYDRATE. J.S. Fleming and J.P. Buyniski. Pharmacology Department, Bristol Laboratories, Syracuse, N.Y., U.S.A.

A potent, new anti-thrombotic agent, 6,7-dichloro-1,2,3,5-tetrahydroimidazo[2,1-b]quinazolin-2-one hydrochloride monohydrate (BL-4162A) has been evaluated for activity against induced platelet aggregation in a series of *in vitro* and *ex vivo* experiments using platelet rich plasma (PRP) from various species including man. In addition, the compound's potential utility as an antithrombotic agent has been tested in various *in vivo* animal models including two models of induced thrombosis involving both large and small vessels. Aggregometry was employed to test the ability of BL-4162A to inhibit platelet aggregation induced by aggregating agents such as ADP, collagen, thrombin and antigen-antibody complexes. The compound's antithrombotic activity was evaluated in small vessels using the biolaser-rabbit ear chamber technique while the effect of BL-4162A on large vessel thrombosis was assessed against electrically-induced carotid artery thrombosis in dogs. Results indicate that BL-4162A inhibits platelet aggregation in the range of 0.08 to 0.68 µg/ml. Platelet antiaggregating activity was also observed in *ex vivo* aggregometry studies in dogs and rats at oral doses in the range of 1 to 10 mg/kg. Of particular interest, is the fact that BL-4162A effectively inhibited thrombosis in both animal models employed over the same oral dosage range. Results of the above investigations as well as an appreciable duration of action suggest that BL-4162A may be an important candidate for clinical evaluation in thromboembolism.

EFFECT OF DIAZEPAM ON PLATELET FUNCTION. A.C. Carvalho, R.W. Colman, R. Vaillancourt, R. Cbral, and R. Anaya. Harvard Medical School and Hematology Unit, Massachusetts General Hospital, Boston, Massachusetts, U.S.A.; Hematology-Oncology Section, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, U.S.A.

Diazepam (Valium) is one of the most prescribed medications in the world. Patients on Diazepam may need platelet function evaluation. Therefore, a study of its effect on both *in vivo* and *in vitro* platelet function was undertaken in 8 normal volunteers. Diazepam (10-40µg/ml) was incubated *in vitro* with platelet rich plasma (250,000/µl) at intervals of 15, 30, 60, 120, and 240 minutes followed by determination of platelet aggregation and ¹⁴C-serotonin release. Fifty percent inhibition of platelet aggregation and release by Diazepam was obtained at 1 hr with epinephrine (p<0.01) and at 2 hrs with ADP (p<0.01), but no significant effect was noted with collagen. The Diazepam inhibitory effect on platelet aggregation and release was overcome by high concentrations of aggregating agents, suggesting that its primary effect is not mediated by inhibition of prostaglandin synthesis.

Following oral ingestion of 5mg of Diazepam, platelet aggregation and ¹⁴C-serotonin release were determined serially (2, 4, 8, 12, 24, and 48 hours) in the 8 normal subjects. After 8 hours, Diazepam inhibited ADP-induced aggregation and release by 39% (p<0.01) and epinephrine by 50% (p<0.01). No significant inhibition of collagen was observed. Forty-eight hours after Diazepam intake, platelet function returned to normal in all subjects.

Our data show that Diazepam impairs both platelet aggregation and release *in vitro* and *in vivo*. Although the effect of Diazepam on *in vivo* hemostasis is still uncertain, our results suggest caution in the interpretation of platelet function testing in patients on this drug.