The effect of the combined oral administration of pentoxifylline (pof) and low dose acetylsalicylic acid (ASA) was evaluated with the help of the laser-induced thrombosis model in rat mesenteric arterioles. Laser-induced thrombosis was inhibited in a dose-dependent way by both drugs. The administration of ASA either simultaneously with or 1 hour prior to pof, does not show any effects in the laser model. On the contrary, the administration of pof followed 1 h later by ASA not only exhibited a significant effect but also produced a supraadditive inhibition of the laser-induced thrombus formation. Specific investigations concerning the time interval between the administration of both drugs determined that a significant effect can be achieved only after an interval of 30 to 90 minutes (principle of HWA 5112).

The striking results could also be shown in diseased animals after consecutive chronic administration of pof 1 h prior to ASA. HWA 5112 exhibits significant effects on laser-induced thrombosis formation in the following chronic animal models: 1. adjuvant arthritic rats, 10 mg/kg for 21 days; 2. spontaneously hypertensive stroke-prone rats (SHR), age 3 months (2.15-7.30) (4.00-8.30) (3.80-9.00) (3.00-7.00) 2 hr after the first (Day 1) and the last dose (Day 8). In 7 subjects 8T was measured also 7 days after the suspension of the drug (Day 15). Before and 2 hr after the first dose (Baseline), 2 hr after the first (Day 1) and the last dose (Day 8). In 7 subjects BT was measured also 7 days after the suspension of the drug (Day 15). Before and 2 hr after the first dose, protrombin time (PT), partial thromboplastin time (PTT), thrombin time (TT), PA and the RR induced by different concentrations of ADP, PAF-activator, collagen (coll), epinephrine (epi), arachidonic acid (AA) were studied. BT was significantly prolonged after vitamin B6 administration, and returned to baseline values 7 days after suspension of the drug. PA and the RR induced by 1 uM ADP, 1 uM/100 ml collagen or 5 uM epinephrine were significantly inhibited 2 hours after vitamin B6 administration. Vitamin B6, however, did not affect PA or the RR induced by 0.2-2 uM PAF-activator, 2 uM ADP, 1 uM AA, 2 uM/100 ml collagen, nor did it affect PT, PTT or TT. These data show that orally administered vitamin B6 impairs primary hemostasis, but does not affect fibrin formation, as measured with standard coagulation tests.

**Platelet Inhibitors**

**Effects of Inhibitors on Collagen Induced Platelet Aggregation in Six Different Species.** J.W.G.M. Jansen-Duphar b.v., Dept. of Pharmacology, P.O. Box 2, 1380 AA Wempe, The Netherlands.

One approach to the development of antithrombosis is inhibition of platelet aggregation. The pharmacological approach often used is to test compounds on collagen induced platelet aggregation measured in platelet rich plasma. Therefore we have compared inhibitors with different mechanism of action on aggregation of platelets from six different species commonly used in pharmacological studies. Aggregation was induced with submaximal amounts of collagen (Hormone Chemie).

Inhibitors of the cyclooxygenase system, aspirin and indomethacin, were very potent in inhibiting aggregation of platelets from guinea pig and dog (IC50 20-60 and 1-3 uM resp.). Aggregation of pig and rat platelets was poorly inhibited by both of these compounds (IC50 700-900 uM), whereas platelets from mice showed intermediate sensitivity (IC50 ca. 100 uM).

The combined lipooxygenase/cyclooxygenase inhibitor BW755C, was extremely active on platelets of guinea pig (IC50 1 uM) and poorly active in mice platelets (IC50 300 uM). In the other species the inhibitory activity ranged from 20-80 uM.

The phosphodiesterase inhibitors, papaverine and BL3459 inhibited aggregation in all species (IC50 50-100 and 1-5 uM resp.). Dipryridamole inhibited aggregation also in all species but with lower activity (IC50 >100 uM).

Conclusion: remarkable species differences are present with respect to inhibition of collagen induced platelet aggregation by the various compounds e.g. rat and porcine platelet aggregation was hardly inhibited by cyclooxygenase inhibitors. The effects of the compounds on human platelets are comparable to the effects on canine platelets.