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SYNVINOLIN (SYN) IN TYPE IIa HYPERLIPOPROTEINAEMIA : NORMALIZED PLATELET HYPERREACTIVITY ASSOCIATED WITH AN IMPROVED RESPONSIVENESS AGAINST PGI_2 AND ENHANCED PGI_2 RECEPTORS. K. Schrör (1), P. Löbel (1) and E. Steinhagen-Thiessen (2). Institut für Pharmakologie der Universität Düsseldorf (1) and Medizinische Klinik der Universität Hamburg (2), F.R.G.

Patients with familial hyperlipoproteinaemia (HLP) are at high risk for the premature development of atherosclerosis. This study was designed to investigate the effect of long-term treatment (8 months) with the HMG-CoA-reductase inhibitor SYN (20-40 mg/day) on platelet reactivity and PGI_2 receptors in 12 HLP patients (B) as compared with 11 untreated HLP patients (A) and 11 healthy subjects (C). Treatment with SYN reduced the plasma cholesterol to 234 ± 12 mg/dl as compared to 307 ± 21 (A) and 195 ± 14 mg/dl (C), respectively. Collagen (0.6 µg/ml) induced platelet thromboxane (TXB_2) formation was 50 ± 6 ng/ml in group A and significantly reduced to 32 ± 3 (B) which was not different from the 28 ± 3 ng/ml in group C. Similar results were obtained by measuring platelet ATP secretion and aggregation. SYN treatment significantly improved the reduced number of PGI_2 receptors (determined according to Schillinger & Prior, 1980) and normalized the iloprost (ILO, 30 nM) induced cAMP stimulation in platelet-rich plasma while the k_D remained unchanged:

Parameter	Control	HLP	HLP + SYN
B_{max} (fmol/mg protein)	121 ± 6	56 ± 7	84 ± 3
k_D (nmoles/l)	38 ± 3	31 ± 2	24 ± 4
ILO-stimulated cAMP (pmol/ml)	135 ± 7	78 ± 6	131 ± 17
number of pooled samples	5	3	3

These data demonstrate that SYN-treatment of HLP patients at doses that reduce plasma cholesterol by about 25% results in sigficant improvement of platelet function. This includes both normalization of platelet hyperreactivity against proaggregatory agents as well as platelet hyporeactivity aganist PGI_2. The last effect might involve an increase of the (reduced) number of PGI_2 receptors in HLP type IIa.

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PREVENTION OF SYSTEMIC THROMBO-EMBOLISM IN PATIENTS WITH ATHEROSCLEROTIC INTERMITTENT CLAUDICATION.

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Ticlopidine (TI), an anti-aggregating agent which inhibits the ADP-pathway has been tested in patients with intermittent claudication (IC) in 11 randomized clinical trials (RTCs).

As expected, a significant reduction of cardio-vascular events (CVE) due to systemic thrombo-embolism was observed in the 2 larger. Reduction in the number of CVE due to systemic thrombo-embolism in any arterial bed was observed. This prompted us to confirm the hypothesis that TI was beneficial in preventing systemic thrombo-embolism in patients with IC. Four RCTs from the 11 were blindly selected on the basis on pre-set selection criteria : placebo controlled, more than 1 month duration, less than 5 % lost-to-follow-up (index of quality), parallel groups, proven atherosclerotic disease. Meta-analysis was performed with 5 statistical methods which gave consistent findings : as compared to 311 patients on placebo, the 301 patients on TI have had a 66 % reduction in the number of CVE during the 6 months of follow-up (9.0 % to 3 % , p = 0.002). Walking distance, a secondary objective of meta-analysis, doubled in 42 % of the patients on TI as against 27 % (p = 0.0005).

It was concluded that TI 250 mg b.i.d. prevents CVE in patients with atherosclerotic IC.

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GEMFIBROZIL HAS ANTI-PLATELET EFFECTS IN PATIENTS WITH HYPERCHOLESTEROLAEMIA DURING PHYSICAL STRESS

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Earlier studies indicate an increased platelet reactivity in patients with hypercholesterolaemia. Physical and mental stress have also been reported to cause increased reactivity. The present study was undertaken to evaluate the effect of gemfibrozil (G) a new lipid lowering drug on platelet reactivity during physical stress. Ten otherwise healthy male subjects with serum cholesterol levels above 7 mmol/l were involved in a double-blind study. It consisted of two treatment periods of 8 weeks during which the patients were given either G (600 mg b.i.d.) or placebo (Pl) and an 8 weeks wash-out period before the cross-over. At the end of the treatment periods an exercise test was carried out and platelet reactivity tested. Adrenaline, ADP and collagen were used to induce aggregation and 5-HT and TxB_2 release measured. Plasma beta-TG and fibrinogen were also determined. The treshold concentration of adrenaline necessary to evoke secondary aggregation was increased in 8/10 patients during exercise after G treatment and in 2/10 after Pl. When the lowest ADP concentration to cause secondary aggregation (2-4 uM) was used there was a significant decrease in the 5-HT (- 44%) and TxB_2 (- 48%) secretion and a significant decrease in the area under the aggregation curve (- 28%). A decrease in 5-HT secretion was also seen after G treatment when a fixed ADP concentration of 10 uM was used. During collagen stimulation no changes were seen between the two groups. Beta-TG remained unchanged irrespective of treatment and fibrinogen showed a modest increase during exercise in both treatment groups. These results indicate a new anti-platelet effect of gemfibrozil which might be of importance in prevention of acute thrombotic events in hypercholesterolaemic patients.

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ANTI-THROMBOTIC EFFECT IN CANINE CORONARY ARTERIES OF A COMBINED TXA_2 SYNTHETASE/TXA_2-PROSTAGLANDIN ENDOPEROXIDE RECEPTOR INHIBITOR (R 68070).

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The effects of R 68070, an oxime-alkane carboxylic acid derivative combining specific thromboxane A_2 (TXA_2) synthetase inhibition with TXA_2/prostaglandin endoperoxide receptor blockade in one molecule, on thrombus formation in a coronary artery following electrically-induced endothelial injury and on its myocardial repercussions were examined in dogs. In an open-chest model in anaesthetized dogs, a stainless steel electrode was inserted into the left anterior descending coronary artery (LAD) distally (± 1 cm) from an electromagnetic flow probe. ECG and heart rate were derived from limb leads. Serum TXB_2 levels were measured by RIA on venous spontaneously coagulated blood (1 h, 37°C). Endothelial cell injury in the LAD coronary artery was induced by the application of an anodal current of 300 µA during 30 min; after an additional 60 min observation period, the thrombus wet weight was determined. In comparison with solvent treatment (n = 8), R 68070 (1.25 mg/kg I.V. 10 min before electrical stimulation, n = 7), significantly reduced the thrombus mass (solvent : 43 mg; R 68070 : 18 mg median value, p < 0.05), the incidence of ECG changes indicative for myocardial ischemia (fibrillation : solvent 1/8; R 68070 0/7; arrhythmias : solvent 3/8; R 68070 2/7; ST changes : solvent 7/8; R 68070 1/7, p < 0.05) and the decrease in coronary blood flow after electrical stimulation (solvent : from 13 to 6.5 ml/min; R 68070 : from 13 to 11 ml/min median values, p < 0.05). Serum TXB_2 levels were reduced by 92 % at 100 min after the injection of the active compound (median value, n = 7).
Heart rate and coronary blood flow measured before the induction of the endothelial injury were not modified by R 68070.
The present study thus demostrates that R 68070 exerts a potent anti-thrombotic effect in canine coronary arteries. The relative contributions to this effect of TXA_2 synthetase inhibition and of TXA_2/prostaglandin endoperoxide receptor blockade exerted by the compound are being investigated.