2024

EFFECT OF ANTIAGGREGANT ON OCCLUSION OF SAPHENOUS GRAFT CORONARY BYPASS.

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Double blind study on 49 patients, 24 receiving aspirine-dipyridamole, 25 a placebo. In both groups 20 patients were followed during one year. The two groups did not differ according to age, sex and number of coronary bypass. In all the patients, Calparin (3 x 5000 U/day) was injected subcutanously the day before and the 7 days after surgery. In the first group dipyridamole (25 mg/kg) was injected during the same period. The second group received a placebo IV injection. Thereafter long acting dipyridamole (400 mg/day) and aspirin (200 mg/day) were given orally in the first group, placebo in the second one. Cardiac follow-up included E.C.G. and thallium at maximum exercise. Coronarography was performed only in case of reappearence of chest pain. No difference was found between the two groups for the coagulation parameters during the whole year of study. Statistically significant differences between the two groups were found during the same period for β-thromboglobulin, fibrino-peptide A and the ratio $\Delta^+\beta$TG/Δ^+ FPA. Platelet activity, elevated in the placebo group, was kept in normal limits in the treated group. During the two first months for the placebo and during the first month for the treated group the ratio $\Delta^+\beta$TG/Δ^+ FPA decreased in all patients showing the importance at this time of plasmatic hypercoagulability compared to platelet hyperactivity. During the 12 months of the study 5 thrombotic accidents (25 %) were noted in the placebo group (2 myocardial infarctions, 2 occlusions of bypass, 1 caseof cerebral arterial disease) and 2 (10 % in the treated group) (1 postoperative death, 1 myocardial infarction) (NS ; p =•0,21). Our results lead to two conclusions :
1) Platelet antiaggregants may influence the permeability of saphenous graft coronary bypass. A careful study of platelet activity with eventual change of the drug used may improve the late results of surgery.
2) Association of anticoagulant therapy (anti-vitamin K) during the two first months after surgery could also be useful.

2025

EFFICACY OF INTRAVENOUS PENTOXIFYLLINE IN THE MANAGEMENT OF PATIENTS WITH CRITICAL LEG ISCHEMIA.

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The xantine derivative pentoxifylline (P) can promote blood flow in the macro-and-micro circulation of ischemic tissues by improvement of red cell rigidity and by enhancing PGI_2 release from the vascular endothelium. 35 patients (mean age 71±1.2 1SE years) suffering from critical leg ischemia due to advanced peripheral vascular disease (PVD) were treated by continuous I.V. drip of P (mean dose 22.2 g. during a mean period of 22.2 days). 19 patients were diabetics and 16 non-diabetics. Severity of PVD was assessed by the walking distance (WD), the presence of ischemic rest pain (IRP), leg ulcers or gangrene (doccumented photographically), hemodynamic evaluation using Doppler auscultation and by an arteriography of the lower limbs. The most common lesion on arteriography was occlusion or severe stenosis of the superficial femoral artery. All the patients suffered from IRP, 20 of them from leg ulcers and or gangrene. Following treatment of the diabetics, the WD was considerably improved ($p<0.01$) in 7 patients, the IRP disappeared in 11 and was milder in another 4 patients. Leg ulcers were healed in 5 out of 11 patients and gangrene subsided in 2 out of 9 patients. It was partially healed in another 3 patients. Thus only in 4 patients the leg ischemia was worse and required bellow-knee amputation. In the non-diabetics, WD was improved considerably in 12 patients, the IRP disappeared in 11 and was milder in another 4 patients. Gangrene subsided in 2 out of 4 patients and was improved in the remaining 2 patients. None of these patients underwent amputation. The resting ankle pressure index (on Doppler auscultation) values were similar in the 2 groups and were increased after treatment ($p<0.01$).

Our results indicate that P ia a useful drug in the management of patients with advanced PVD and critical leg ischemia particularly in non-diabetics. It should be considered in inoperable patients in whom leg amputation is imminent. P can induce both subjective and objective improvement in the WD and the hemodynamic profile of these patients and promote the blood flow in the microciculation of the ischemic tissues in the lower limbs.

2026

DIPYRIDAMOLE INHIBITS PLATELET FUNCTION IF SUFFICIENTLY HIGH PLASMA LEVELS ARE REACHED.

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Dipyridamole is widely used as a platelet function inhibiting drug. It is effective in some animal thrombosis models. In healthy volunteers we studied the plasma levels after ingestion of 2 x 75 mg Dipyridamole using a fluorometric assay. We found a large variation of individual resorption rates. The highest plasma levels were detected between 30 and 60 min after intake ranging from 0,9 to 2,28 mcg/ml. Platelet retention and the percentage of stimulated platelets after addition of tissue extracts were markedly decreased. Also an increase in stypven time and slight changes in platelet volume distribution were detected during this period. To determine the plasma level of dipyridamole which is necessary to inhibit platelet shape change and to prolong the stypven time we performed a placebo controlled double blind cross over study in 12 healthy volunteers. Blood was drawn before and 2 and 4 h after intake of 150 or 300 mg Dipyridamole over a period of 4 h. Using an initial dose of 37,5 mg followed by administration of 7,5 mg every 15 min mean continuous plasma levels of about 0,65 mcg/ml (2h 0,64 mcg/ml, 4 h 0,668 mcg/ml) were measured. Starting dose of 75 mg followed by multiple doses of 15 mg resulted in mean plasma levels after 2 h of 1,312 and after 4 h of 1,293 mcg/ml. No side effects were observed. The plasma levels varied between the individuals. Dose-dependently a significant inhibition (p 0,01) of tissue extract induced platelet stimulation and a prolongation of stypven time was observed. The antithrombotic effect of Dipyridamole is not correlated with the inhibition of platelet aggregation, but may be closely related to the inhibition of platelet adhesion and platelet factor 3 availability.

2027

AN EXTRACT OF FEVERFEW INHIBITS INTERACTION OF HUMAN PLATELETS WITH COLLAGEN SUBSTRATES.

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Feverfew (Tanacetum parthenium) has been used since ancient times as a herbal remedy for migraine, fever and arthritis. Recently it has been shown that extracts of feverfew inhibit aggregatory and secretory responses in human platelets induced by various soluble agonists.

The interaction of platelets with surfaces coated with human collagens of type III (C III) and IV (C IV) has been studied by measuring the deposition of 51-Cr-labelled platelets and by scanning electron microscopy. Experiments were performed using platelet-rich plasma (PRP) and suspensions of gel-filtered platelets. Platelets were deposited on C III mostly as surface-bound aggregates. In contrast they were deposited on C IV mostly as spread forms of individual cells. Formation of aggregates on C III was more extensive for PRP than for GFP; in contrast platelet spreading on C IV was more extensive for GFP than for PRP.

Feverfew extract inhibited the deposition of 51-Cr-labelled platelets on both C III and C IV in a dose dependent way. Similar concentrations of extract were needed to inhibit the formation of surface-bound aggregates and to inhibit platelet spreading in both PRP and GFP.

The results indicate that feverfew may have antithrombotic potential in addition to its claimed benefit in certain clinical conditions.