Blood platelets and vascular walls generate prostaglandin (PG) derivatives with opposing effects. Since aspirin (ASA) inhibits synthesis of common precursors of these derivatives, the rationale for its clinical use in thrombosis prevention trials has been questioned. This is an experimental approach to this important therapeutic dilemma. Male CD rats (250–350g) were given a single i.p. dose of ASA (0.5–200mg/kg) and killed from 1 to 120 hrs thereafter. Platelet PG production was measured by a thioribarbiturate assay of malondialdehyde (MDA) under thrombin (25u/ml) stimulation. Vascular PG activity released from rings of abdominal aorta and inferior vena cava was determined as platelet aggregation inhibitory potency and characterized as PGI2 by standard criteria. The inhibitory effect of ASA lasted longer in platelets (90-120 h) than in venous (24-48 h) or arterial tissues (ID50=3.6mg/kg) but as sensitive as venous tissues (ID50=2.3mg/kg) when PG synthesis was measured 1 h after treatment. The proposed unique sensitivity of platelet cyclo-oxygenase to ASA therefore needs reconsidering. ASA's effect on various systems might be better dissociated based on the different duration of inhibition. We suggest that the lowest single dose of ASA totally inhibiting platelet PG synthesis should be given at the longest possible intervals.

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PG12 production and its inhibition by aspirin (ASA) by endothelial cells (EC) and cells of the de-endothelialized vessel wall (non-endothelial cells (NEC)) in arteries (ART) and veins. Segments of ART and veins were obtained from rabbits 15 min, 1,3,6 or 20 hrs after ASA (100 mg/kg, IV). The EC were separated from the vessel wall as a complete monolayer using a cellulose acetate paper/cell adhesion method. PG12 was quantitated by a thrombin-induced 14C-SHT release assay. ART EC produced 1.13 ± 0.12 ng PG12/100 mm² (2.15 ± 0.09 x 10⁵ cells) (mean ± SE, n=18). Vein EC produced 0.52 ± 0.06 ng PG12/100 mm² (1.34 ± 0.08 x 10⁵ cells). After ASA, PG12 production was maximally inhibited in both ART and vein EC for 6 hrs and was almost restored to control levels by 20 hrs. ART and vein NEC produced 1.54 ± 0.15 and 0.77 ± 0.08 ng PG12/100 mm² respectively. After ASA, ART NEC production was maximally inhibited for 6 hrs and was restored to 56% of control levels by 20 hrs. In contrast, PG12 production by vein NEC was maximally inhibited for only 1 hr after ASA and was restored to control levels by 6 hrs. This data demonstrates that vessel wall cells other than EC produce PG12 in both veins and ART and suggests that the turnover of cyclo-oxygenase in vein NEC is more rapid than EC and ART NEC. PG12 production by NEC may be an important source of PG12, particularly when the vessel wall is transected or the EC are removed.

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The effects of two different doses (0.3-1.5 g) of ASA on platelet thromboxane (Tx) and endothelial prostacyclin (PG12) formation have been investigated in 4 healthy adults. Both doses gave a complete suppression of TxB2 formation as measured by radioimmunoassay (RIA) of serum obtained 2 hours after ASA. PG12 production was assessed by a bioassay based on the inhibition of ADP-induced platelet aggregation. The formation of PG12-like inhibitory activity in vein specimens obtained at biopsy was abolished by either dose of ASA. In two subjects taking 0.3 and 1.5 g of ASA respectively, inhibition of PG12 formation was confirmed by measuring 6-keto-PGF1α, the stable hydrolysis product of PG12, by RIA. We have also studied a patient with an "aspirin-like" syndrome characterized by a mild congenital bleeding tendency, defective platelet release reaction, lack of aggregation by arachidonic acid and no TxB2 formation after thrombin. Venous biopsy specimens failed to produce PG12 as measured by both bioassay and RIA. These studies show that the cyclo-oxygenase enzyme systems of human platelets and endothelial cells are both susceptible to inhibition by ASA in vivo; and no difference was noted in the degree of inhibition induced with the two dosages. The congenital deficiency of both PG12 and Tx formation in one patient was associated with a mild bleeding diathesis but no thrombosis tendency.

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0368 Aspirin as a potential antithrombotic drug: an experimental approach for more rational clinical use.

0369 PG12 production and effect of aspirin on endothelial cells and non-endothelial cells of the vessel wall

0370 Aspirin (ASA) inhibits both prostacyclin and thromboxane formation in man