0074
10:00 h

SOME BIOCHEMICAL STUDIES WITH SQ 26271: A STABLE PARTIAL PROSTACYCLIN AGONIST IN THE HUMAN PLATELET. Don N. Harris, Marie B. Phillips, Inge M. Michel, Harold J. Goldenberg, James E. Heikes, Peter W. Sprague, and Michael J.Antonaccio. Departments of Pharmacology and Organic Chemistry, The Squibb Institute for Medical Research, Princeton, New Jersey 08540.

A newly synthesized 9α-homo-9,11-epoxy-5,13-prostadienoic acid analogue, SQ 26271 (8(S)9(S)11(R)12(S)-9,11-epoxy-9α-homo-5(Z),13(E)-15(R)-hydroxyprostadienoic acid) inhibited arachidonic acid (AA)-induced platelet aggregation at concentrations which did not affect thromboxane B_2 (TxB_2) levels with an I_{50} value of 0.25 μM. It also was a potent inhibitor of platelet aggregation caused by collagen, 9,11-AzoPGH_2, SQ 24810 (9,11-epoxy-9α-homo-5(Z),13(E)-15α-hydroxyprostadienoic acid) and epinephrine (secondary phase). However, it had little or no effect on thromboxane or prostaglandin synthetase activities. Moreover, SQ 26271 also inhibited the primary phase of epinephrine- and ADP-induced aggregation. In addition SQ 26271 caused a 3-fold increase in platelet adenylate cyclase activity, partially blocked prostacyclin stimulated adenylate cyclase activity and caused a 6-fold elevation of cyclic AMP levels in intact platelets, which was blocked by SQ 22536 (9-tetrahydro-2-furyl)adenine), an inhibitor of platelet adenylate cyclase activity. Finally, the inhibition of platelet aggregation by SQ 26271 was potentiated by an inhibitor of cyclic AMP phosphodiesterase (SQ 20009, etazolate), and reversed by SQ 22536. The above data indicate that SQ 26271 is a stable partial agonist of the prostacyclin receptor in human blood platelets

0075
10:15 h

A MICROELECTROPHYSIOLOGIC BASIS FOR THE FIBRILLATION RETARDANT EFFECTS OF SULFINPYRAZONE AND SALICYLATE. D.H.S. Iansmith, C.B. Nash, and J.P. Bandura. Depts. of Med. and Pharm., Univ. of Tenn., Memphis, Tenn.

The antagonism of platelet function has been suggested as a mode of action for sudden death prophylaxis by sulfinpyrazone (S) and salicylates (A). To evaluate an antiarrhythmic means for such action, 5.0 to 20.0 mg/Kg A or S was administered i.v. to open-chest, intermittently cardiac paced canines in which arterial pressure and EKG were monitored. Fibrillation thresholds (FT) were measured before and after coronary arterial ligation and drug administration, by extrastimuli of increasing current strength during the vulnerable period of the T wave. Acutely both A and S increased FT 2 to 3 times that of post-infarcted values. To elucidate the mechanism for this response Purkinje fibers were isolated from the left ventricles of adult canines. These were pinned to the paraffin floor of a lucite isolation well, affixed with stimulating and surface recording electrodes, and partitioned with a plastic collar coated with vegetable fat to provide a fluid seal. Separate inflow and outflow ports allowed for individualized microenvironments for each chamber. After 60 min of tissue equilibration with well oxygenated, 36°C normal Tyrode Solution (TS), the fluid of the chamber distal to the stimulus source was altered to include 2-35 mg% A or 2-50 ugm/ml S, with or without CO_2 substitution for O_2 (pH 6.4) or HCl (pH 6.4). Action potentials (AP) from each chamber were monitored during 60 min of altered TS and then 60 min of normal TS reperfusion. In a dose-dependent manner A depressed AP parameters to cause automaticity and inactivity, while S was without effect. Whereas S was able to prolong tissue survival and support electrical activity in a situation of local acidosis (if absolute hypoxia were not superimposed), A was not. Such information suggests that although both A and S are arrhythmia retardant in the post-infarction period, their modes of action may differ. Both might act as "membrane stabilizers"; however, it appears that electrogenic aberration is necessary before S manifests an effect.

0076
10:30 h

PROTECTION AGAINST EPINEPHRINE EXACERBATED PLATELET THROMBI FORMATION IN STENOSED DOG CORONARY ARTERIES WITH CHLORPROMAZINE. J. Folts. Department of Medicine, University of Wisconsin, Madison, WI.

We have previously shown that platelet thrombi (PTH) form in stenosed canine coronary arteries in five to ten minutes producing reductions in coronary flow (RCF) and that these can be exacerbated by IV infusions of epinephrine (E) by an alpha adrenergic mechanism in spite of pretreatment with aspirin, indomethacin, ibuprofen, or sulfinpyrazone. We have also shown an apparent active involvement of lysed red blood cells (RBC) packed together proximal and in the area of stenosis releasing ADP and exacerbating the PTH formation. On high magnification using carstairs stain and fluoresceine conjugated antisera, fused platelets, lysed RBCs and some fibrin are noted. Eight dogs were prepared with an EMF probe in the circumflex coronary artery along with a fixed mechanical stenosis of 75% of the artery. RCF were noted and 5 ug of E/minute for ten minutes IV raised arterial blood pressure (ABP) 15 ± 6 mm Hg and exacerbated RCF in all dogs, but after administration of .6 mg/kg of chlorpromazine (C) IV the RCF were abolished and repeated infusions of E did not provoke RCA but did lower ABP 10 ± 6 mm Hg. In vitro platelet aggregation (ADP stimulus) decreased from 61 ± 11 LTU to 39 ± 13 LTU ($p < .05$). Red cell osmotic fragility tests were done on samples obtained before and after C and the curve was significantly shifted to the right after C suggesting more stable RBC membranes. We postulate that C may stabilize RBCs, preventing ADP release and inhibit platelet aggregation by an alpha adrenergic mechanism. C or an agent like it may prevent PTH from forming in patients with stenosed coronary or cerebral arteries who smoke or otherwise have elevated plasma E.

0077
10:45 h

SULPHINPYRAZONE DOES NOT INFLUENCE REJECTION OF RENAL TRANSPLANTS. J.H. Turney, M. Bewick, M.J. Weston. Renal Unit, King's College Hospital, London, U.K.

Platelet-mediated intravascular fibrin deposition may be the distal arm of the transplant rejection process. There have been reports that antiplatelet drugs may prevent ameliorate, or even reverse renal transplant rejection. 50 consecutive cadaveric renal transplant recipients were randomly allocated to receive sulphinpyrazone 400 mg twice daily or no treatment additional to conventional immunosuppressive therapy. Patients were followed for 6 months, at which time they were assessed for graft survival and function, and for the number of rejection episodes. Rejection was defined as a rise in serum creatinine for which no other explanation was identified. Results were analysed by the Chi-squared test with Yates' correction. Results at 6 months:

	Anturan	Controls
Total Number	25	25
Total Alive	21	21
Functioning Grafts	14	16
Rejection Episodes	81	68

There were no differences between the two groups, neither did the function of the surviving grafts differ.

We conclude that, in this study, antiplatelet therapy with sulphinpyrazone does not affect the outcome of cadaveric renal transplantation.