

## Supplementary Abstracts

## Thromboxane and Prostaglandins

THE EFFECTS OF CHEMICAL ALTERATIONS OF THE BENZOIC ACID NUCLEUS ON PLATELET FUNCTION AND PROSTACYCLIN ACTIVITY IN THE ARTERIAL WALL. B.A. Killackey, J.J. Killackey and R.B. Philp. Department of Pharmacology, University of Western Ontario, London, Ontario, Canada.

The effects of a series of benzoic acid derivatives (ASA analogs) on prostacyclin (PGI<sub>2</sub>) synthesis by rabbit aorta rings and on human platelet function were examined to determine if antiplatelet activity could be separated from anti-PGI<sub>2</sub> activity.

Rings of rabbit aorta were incubated with or without drugs in Tris 0.05 M, pH 7.5 for 6 m at room temperature (R.T.). Supernatant was then transferred to platelet-rich plasma incubated at 37°C for 3 m. ADP was added 60 s later and aggregation was measured and compared to controls. Rings were also incubated with <sup>14</sup>C-arachidonic acid (<sup>14</sup>C-AA) for 60 m at R.T. in Tris with or without drugs. Products were extracted and measured by radio-T.L.C. along with known standards. Platelet aggregation and release of ATP were measured using a ChronoLog Lumi aggregometer. The effects of these agents on PGI<sub>2</sub> activity were similar to their effects on platelet aggregation. ASA however did not exhibit the marked inhibitory potency that it had on the second phase of platelet aggregation and ATP release. Changing the 2-acetoxy group of A.S.A. to a 2-acetyl or 3-propionyloxy resulted in a loss of inhibitory activity in both systems. 2-Propionyloxy substitution resulted in a similar spectrum of activity to ASA. The effects of these agents on the metabolism of <sup>14</sup>C-AA by rabbit aorta rings generally confirmed the bioassay results although some of the agents had novel effects on blood vessel arachidonic acid metabolism.

Despite potential species differences, this study demonstrates an inability to separate antiplatelet and anti-PGI<sub>2</sub> effects with this series of benzoic acid derivatives. Further study of the effects of these agents on the metabolism of <sup>14</sup>C-AA by rings of rabbit aorta may lead to a better understanding of PGI<sub>2</sub> formation.

## 1418

EFFECT OF IBUPROFEN COMBINED WITH PROSTACYCLIN ON PLATELET AND LEUKOCYTE COUNTS FOLLOWING ACID ASPIRATION INJURY. D. Shepro\*, T. Utsunomiya, M.M. Krausz and H.B. Hechtman. Biological Science Center, Boston University\* and Harvard Medical School, Boston, MA.

Thrombogenesis and certain aspects of inflammation are mediated by products of the arachidonic acid enzymatic cascade, such as prostacyclin (PGI<sub>2</sub>) and thromboxane A<sub>2</sub> (TxA<sub>2</sub>). A ratio of these mediators has been theorized to be significant for modulating platelet and leukocyte activity. It has also been suggested that endothelial cell disruption or dysfunction will alter the titers of PGI<sub>2</sub> and TxA<sub>2</sub>. Acid aspiration in dogs results in respiratory failure with a concomitant entrapment of platelets and leukocytosis. In this study the cyclo-oxygenase inhibitor ibuprofen and PGI<sub>2</sub>, separately or together, were given IV to dogs after endotracheal instillation of 3.0 ml, 0.1 N HCl, and the effects on platelet and leukocyte (WBC) counts over a period of 4 h were quantitated. At 0.5 h platelet counts fell ~25% to 160,800/mm<sup>3</sup> (p < 0.05) and continued to fall (~30% loss) over the course of 4 h. WBC counts increased gradually from ~5,700/mm<sup>3</sup> to ~14,000/mm<sup>3</sup> during the 4 h of observation (p < 0.025). An infusion of PGI<sub>2</sub> (100 ng/kg·min<sup>-1</sup>; n=6) or an IV bolus of ibuprofen (12 mg/kg; n=6) given 1 h post-aspiration had no effect on either platelet or WBC counts in aspirated animals when compared with untreated controls. Six dogs received, 1 h post-aspiration, ibuprofen (12 mg/kg) in an IV bolus combined with a low dose of PGI<sub>2</sub> (10 ng/kg·min<sup>-1</sup>) infused IV for 1 h. In this experimental group platelet counts returned to baseline values and WBC counts remained above control values. Ibuprofen combined with PGI<sub>2</sub> also was an effective therapy for the aspiration pneumonia, which also suggests that thromboxanes and prostaglandin secretions in some yet to be explained manner mediate platelet and/or leukocyte secretions which enhance lung injury.

## 1419

COMPARATIVE EFFECTS OF IBUPROFEN (MOTRIN) ON PROSTACYCLIN AND THROMBOXANE PRODUCTION. W.M. Parks, J.C. Heak, R.L. Czervionke, and D.L. Haycraft. Department of Medicine, University of Iowa, Iowa City, IA.

Ibuprofen (Ibu) has potential as an anti-thrombotic agent with ability to inhibit platelet thromboxane A<sub>2</sub> (TXA<sub>2</sub>) synthesis and to protect the ischemic myocardium. We have evaluated the effect of Ibu on prostacyclin (PGI<sub>2</sub>) production by primary cultures of human umbilical vein endothelium and TXA<sub>2</sub> production by washed human platelets. Radioimmunoassays for 6-keto-PGF<sub>1α</sub> and TXB<sub>2</sub>, the stable end-products of PGI<sub>2</sub> and TXA<sub>2</sub> were employed. Bovine thrombin 0.33 U/ml was used as the stimulus for prostaglandin synthesis. Endothelial and platelet function was assessed using platelet adherence with <sup>51</sup>Cr-platelets to cell monolayers and platelet aggregometry. Both platelets and endothelium exhibited a similar sensitivity to Ibu. Complete inhibition of PGI<sub>2</sub> and TXA<sub>2</sub> production was seen after 30 min incubation with 100 μM Ibu, 85% inhibition with 25 μM Ibu and 50% inhibition with 5 μM Ibu. In contrast to aspirin the effect of Ibu was rapidly reversible and PG synthesis in platelets returned within 5 min after removal of Ibu. In the presence of Ibu, the irreversible effect of aspirin upon TXA<sub>2</sub> production was inhibited. When PGI<sub>2</sub> and TXA<sub>2</sub> production was completely inhibited by 100 μM Ibu, thrombin-induced platelet adherence increased from a baseline value of 3% to 27%. After a single oral dose of 400 mg, Ibu produces serum concentrations up to 135 μM. If comparable mechanisms operate in vivo, Ibu has the potential to cause significant inhibition of both PGI<sub>2</sub> and TXA<sub>2</sub> production. Reversal of the effect appears to be prompt, but no significant differential effect upon TXA<sub>2</sub> production, without a similar effect upon PGI<sub>2</sub> production, was observed at any concentration of Ibu tested.