NSAIDs pathology and therapy W17–W20

W17

NON STEROIDAL ANTI INFLAMMATORY DRUGS (NSAIDs) AND SMALL INTESTINAL DAMAGE - PROSPECTIVE CONTROLLED AUTOPSY STUDY. M C Allison, A G Howatson, C J Torrance, F D Lee, R I Russell

Gastroenterology Unit and Department of Pathology, Royal Infirmary, Glasgow. G31 2ER.

Several pieces of evidence link NSAID use with small intestinal damage. The prevalence and morphology of this enteropathy remain unclear because the jejunal and ileal mucosa are not readily amenable to endoscopic inspection and biopsy. We have examined the entire small intestinal mucosal surface from 713 patients who came to autopsy between January 1990 and October 1991. The drug histories were verified with the patients' General Practitioner and hospital records. 249 had used NSAIDs or aspirin during the 6 months prior to death, and of these 74 had been taking NSAIDs regularly for at least 6 months.

The small intestine was opened, washed and inspected. All jejunal and ileal erosions and ulcers were removed for histological examination and appropriate serological and microbiological investigations performed. Only ulcers histologically breaching muscularis were included in the analysis. Ulcers were subdivided into (a) those with a specific cause identified (eg vasculitis), and (b) non-specific ulcers:

	NSAID group (n=249)	Control group (n=464)
Specific ulcers:	4(1.6%)	7(1.5%)
Non-specific ulcers:		
- jejunum	6	0
- ileum	12	3
- throughout	3	0
Total non-specific:	21(8.4%)*	3(0.6%)

* X^2 = 27.8, p<0.001, three perforations in NSAID group.

This study demonstrates a strong association between NSAID use and non-specific small intestinal ulceration. Most cases are subclinical but serious complications may occur. The distal ileum is the most frequently affected.

W18

ENTEROCYTE MITOCHONDRIAL DAMAGE DUE TO NSAID IN THE RAT. S. Somasundaram, AJ Macpherson, J Hayllar, P Saratchandra, I Bjarnason. Departments of Medicine and Clinical Biochemistry, King's College School of Medicine, Bessemer Road, London.

Subcellular studies show highly specific alterations in the activities of mitochondrial and endoplasmic reticulum marker enzymes following NSAID administration in the rat (6h) long before macroscopic or histological damage becomes evident (24h). Our aim was to further characterise the effect of NSAIDs on enterocyte mitochondria. Following a single 30 mg/kg gavage dose of indomethacin rats (N:6-12) were studied at 1, 6 and 24 h. Electron microscopy (1h) showed dramatic ballooning of mitochondria from mid small bowel and less marked changes proximally and distally. These changes were followed by significantly increased activities (*:P< 0.01) of citrate synthase (N:2.1 +/- 0.7, 6h: 2.9 +/- 0.5, 24h: 3.7 +/- 0.5*(μmol/min)M+/- SD) and succinate dehydrogenase(N: 93 +/- 21, 6h: 246 +/- 55*, 24h: 280 +/- 68* (mU/mg DNA)).Histochemical activity stains on frozen sections (N:12) for succinate dehydrogenase and cytochrome oxidase showed that the mitochondrial respiratory chain activity was entirely in enterocytes. These results suggest that indomethacin affects the intestinal enterocyte mitochondria, probably by partially uncoupling of oxidative phosphorylation resulting in mitochondrial swelling. Increased mitochondrial enzyme activity represents a compensatory mitochondrial biogenesis, which is so characteristic of human inflammatory bowel disease, and may explain the protective effect of coadministration of glucose and citrate to minimise indomethacin damage.

W19

SELECTIVE INHIBITION OF RECTAL MUCOSAL THROMBOXANE BY LOW DOSE ASPIRIN: THERAPEUTIC POTENTIAL

Cole A T, L Kurlak, Hawkey C J.

Dept Therapeutics, University Hospital, Nottingham NG7 2UH.

Active colitis is associated with increased thromboxane (TX) B2 synthesis and TX receptor antagonists are therapeutic in animal colitis. Since low dose aspirin selectively inhibits platelet thromboxane synthesis we investigated its effect on human rectal eicosanoid release.

METHODS Twelve normal volunteers (age 20 – 32, 7 male), in a blinded crossover study comparing plain aspirin 75mg and 300mg, enteric coated 300mg aspirin and placebo daily, were studied by 4 hour rectal dialyses before and twice (2 – 6 hours, and 6 – 10 hours) after 5 days of each treatment, using 12 x 0.6cm Visking tubing filled with Rheomacrodex. Dialysate was assayed by radioimmunoassay for TXB2 and PGE2 (validated against GCMS) and LTB4 (validated against HPLC). Data were log transformed and subjected to repeated measures analysis of variance.

RESULTS Pre – treatment values for each study period showed the technique was reproducible (coefficient of variation for TXB2 7.7%, PGE2 12.5%, LTB4 12.5%). All doses of aspirin significantly inhibited TXB2 ($p < 0.05$) from 1.07 ng/ml (geometric mean, 95% confidence interval, 0.77 – 1.49 ng/ml) to 0.78 (0.52 – 1.18) ng/ml with aspirin 75mg, 0.76 (0.51 – 1.14) ng/ml with 300mg and 0.80 (0.54 – 1.12) ng/ml with 300mg enteric coated aspirin, but had no effect on PGE2 or LTB4.

CONCLUSION Aspirin 75 – 300mg daily selectively inhibits rectal mucosal thromboxane production and may have therapeutic potential in inflammatory bowel disease.

W20

PROSTAGLANDINS AND ARACHIDONIC ACID IN COLORECTAL CANCER. C Hendrickse, S Radley, A Davis, MRB Keighley, R Kelly*, J Neoptolemos. Dept of Surgery, University of Birmingham and Dudley Rd Hospital, Birmingham; * MRC Reproductive Biology Unit, Charmers St, Edinburgh.

Experimental studies have suggested a role for prostaglandins in carcinogenesis. Colorectal tumours in man have been found to contain increased amounts of the fatty acid arachidonate (20:4, n-6) in total lipid extracts. This may be of relevance as arachidonate is the precursor of the putative tumour promoting prostaglandins especially PGE_2. We therefore assessed phospholipid fatty acids and prostaglandins in malignant and normal mucosa from 18 patients with colorectal cancer. Fatty acids were measured by gas liquid chromatography and prostaglandins by radioimmunoassay.

The absolute levels (median, range) mg g^{-1} wet weight of arachidonate were increased in the phospholipid fraction from tumours (0.48, 0.23-0.68) compared to normal mucosa (0.34, 0.12-0.58; p=0.0302). As a proportion of total fatty acids present (Relative %) however, there was no significant difference between tumour (9.03, 4.13-13.71) and mucosa (9.3, 4.59-15.5) (NS). The level ng g^{-1} wet weight of prostaglandin PGE_2 was significantly increased in tumour (109, 26-452) compared to normal mucosa (18.5, 7.7-111.2; p <0.005). PGF_2 levels in tumour (48, 13.9-213.1) and mucosa (41.8, 6.5-338.9) were not significantly different.

Prostaglandin PGE_2 are increased in colorectal tumours, this elevated prostaglandin level is probably a reflection of phospholipase activity rather than substrate availability and is suggestive of a role for prostaglandins in carcinogenesis.