T185

## ORNITHINE DECARBOXYLASE ACTIVITY IN CACO-2 CELLS: EFFECT OF NORMAL AND POLYPOSIS BILE.

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The clustering of duodenal adenomas and cancers around the ampulla of Vater in patients with familial adenomatous polyposis (FAP) suggests that bile is important in the development of these tumours. Several reports indicate that this may be due to the greater carcinogenic potential of bile from polyposis patients. The aim of this study was to examine the effect of bile from polyposis patients (n=5) and from control patients (n=5) on the induction of ornithine decarboxylase (ODC) activity in a colorectal cancer cell line (Caco-2). Caco-2 cells were incubated for 4 hours in medium with and without FAP bile or normal bile at a concentration of 1:500(vol/vol). Gastrin (50μg/ml), a known inducer of ODC in Caco-2 cells was used as a positive control. Following incubation, medium was decanted and cells scraped and sonicated. ODC activity was measured using a [$^{14}$C]-ornithine bioassay and results expressed in pmol/mg protein/h.

**Results**

| | n | Median | Range |
|---|---|---|---|
| Caco-2 control | 12 | 87 | 25-121 |
| Caco-2 + normal bile | 12 | 243 | 55-532 |
| Caco-2 + FAP bile | 12 | 169 | 97-629 |
| Caco-2 + gastrin | 12 | 440 | 350-665 |

FAP bile and normal bile significantly increase ODC activity when compared to control ($p<0.02$). However, no significant difference between FAP bile and normal bile was observed ($p=0.4$). Induction of ODC with bile was significantly less than that observed with gastrin ($p<0.01$). These results suggest that the ability of bile to stimulate polyamine production is not further enhanced by bile from polyposis patients.

T186

## MANIPULATION OF THE RETICULOENDOTHELIAL SYSTEM:- EFFECTS ON THE GROWTH OF LIVER TUMOUR.

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The prognosis for patients with liver metastases remains poor. We have developed an animal model of liver metastases using a cell line derived from a colonic carcinoma. Using this model we have shown that Octreotide, a long acting somatostatin analogue is effective in inhibiting tumour growth. Octreotide is a potent stimulator of hepatic reticuloendothelial (RES) activity and this may be the mechanism of action. Gadolinium chloride (GAD) is a well known RES toxin, which effectively blocks hepatic RES activity. We have used GAD in combination with octreotide to assess the effect of RES blockade.

Twenty-four BDIX rats received an IV injection of GAD (5mg\Kg), and 24 animals an equivalent volume of saline. All animals then received an intraportal injection of $1x10^7$ K12\Tr cells. Half of the GAD treated rats received octreotide (2ug sc bd) for 4 weeks, and the remainder saline. At 4 weeks the amount of liver tumour present in each group was determined by % hepatic replacement: saline and saline(control) median 17.5% (range 5.7-24.2), saline and Octreotide 0.6% (0-2.5), GAD and saline 42% (21.2-68) and GAD and Octreotide 11.2% (1.9-32.4). These results show that RES blockade with GAD significantly (Mann Whitney U $p<0.01$) increases tumour growth compared to controls. Octreotide significantly reduces tumour growth but is more effective in the absence of GAD. These observations suggest that 1) RES activity is important in the growth of liver metastases and 2) the efficacy of octreotide in inhibiting the growth of hepatic tumour may be partly dependant on a functioning RES system, but other mechanisms are also involved.

T187

## RANITIDINE BISMUTH CITRATE IN THE PREVENTION OF ASPIRIN – INDUCED GASTRIC MUCOSAL INJURY.

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The aim of this study was to evaluate the ability of a new compound ranitidine bismuth citrate (RBC) to protect human gastric mucosa from aspirin – induced damage.

METHODS: Twenty – four male volunteers (mean age 22 years SD 2.6) participated in a randomised, double blind, placebo controlled, 3 way crossover trial in which they received 9 doses of placebo, and aspirin 900 mg bd both with or without RBC 800mg bd. Endoscopy was performed prior to each treatment, on day 1 and 5 and the number of gastric haemorrhagic and non haemorrhagic erosions counted. The stomach was washed and aspirated at each endoscopy and gastric microbleeding determined by the orthotolidine reaction.

RESULTS:

| | Number of erosions Median* (IQR) Haemorrhagic | Non – haemorrhagic | Microbleeding(ul/10min) Median* (IQR) |
|---|---|---|---|
| Placebo | 0 (0 – 2) | 0 (0 – 0) | 0.36 ( – 0.28 – 0.9) |
| Aspirin | 18 (12 – 30) | 2 (0 – 4) | 11.28 (4.89 – 20.7) |
| Aspirin + RBC | 0 (0 – 1) | 0 (0 – 3) | 0.38 ( – 0.29 – 0.79) |

Aspirin vs aspirin + RBC $p<0.001$, $p=0.057$, $p=0.005$
* change from baseline endoscopy

CONCLUSIONS: RBC confers substantial mucosal protection against aspirin – induced gastric mucosal damage.

T188

## ULTRASOUND IS A USEFUL INITIAL INVESTIGATION IN DYSPEPSIA

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Abdominal ultrasound(US) can detect upper gastrointestinal pathology relevant to dyspepsia.We have examined its efficacy as an initial screening investigation.

Subjects:120 new subjects with dyspepsia (68F, mean age 46, range 16-95) had abdominal US performed on the same day prior to OGD. .

Results:OGD discovered 6 cases of oesophagitis, 3 gastric ulcers (GU), 2 gastric carcinomas (CA), and 9 duodenal ulcers (DU). US correctly identified all CAs and GUs and 2 DUs. One DUwas identified as an antral ulcer, 2 as duodenal thickening, 2 as antral thickening, one was normal on ultrasound and in one there was inadequate visualisation. 2 cases of oesophagitis were missed. OGD was said to be required if any gastro-duodenal mucosal abnormality was detected by US, 54/120 subjects(45%) of endoscopies would have been saved and 94% of pathology picked up (only one DU missed). In addition, 13 cases of gallstones, 4 cases of possible pancreatitis, and 1 renal calculus were detected on ultrasound (only one of whom had significant pathology on OGD).

Conclusion US contributed to the diagnosis of dyspepsia in 18/120 (15%) of cases (12 normal on OGD) and detected additional pathology (8 fatty livers, 1 ovarian cyst, 1 prostatic tumor, and 2 cases of renal cysts). US can accurately diagnose gastric lesions, but is less reliable at detecting DU. It can however detect duodenal pathology from duodenal wall thickening and/or associated gastric pathology. It may be a more rational and cost effective initial investigation in dyspepsia.

T189

## EFFECT OF RANITIDINE BISMUTH CITRATE ON MEAL-STIMULATED GASTRIN RELEASE

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This study compared the effect of ranitidine bismuth citrate (RBC) with an equipotent dose of ranitidine, to determine whether RBC's bismuth content, by an anti-*Helicobacter pylori* activity, would counteract ranitidine's gastrin raising anti-secretory activity
METHODS: 24 male patients with present or past duodenal ulceration (age range 23-66), who had taken no anti-secretory drug for 2 weeks and no bismuth compound for 3 months, were studied before and on the seventh day of dosing with either RBC 800mg b.d. or ranitidine 300mg b.d. (double-blind, randomised, parallel groups). Breakfast was given at 0815; the blood samples were taken hourly from 0800h to 1200h for plasma gastrin concentration (measured by radioimmunoassay), and at 1200h a $^{13}C$ urea breath test was performed. The breath test was considered positive if there was an excess of $^{13}CO_2 > 5$ per mil.
RESULTS: The medication was well tolerated; no major adverse effects were reported. The $^{13}C$ urea breath tests were positive in 21 patients and remained positive in 9/9 of the ranitidine-treated patients, whereas only 2/12 patients treated with ranitidine bismuth citrate remained positive.
**Mean integrated plasma gastrin 0800-1200h (pmol/L):**

| | Before | After |
|---|---|---|
| Ranitidine (n=12) | 15.9 | 26.8 |
| RBC (n=12) | 27.1 | 39.3 |

There was no significant difference between treatment groups
CONCLUSIONS: The expected rise in meal-stimulated plasma gastrin with ranitidine was seen in the 12 patients who received ranitidine, but despite the effective suppression of *H.pylori* urease activity in 10/12 patients taking ranitidine bismuth citrate, there was no attenuation of the meal-stimulated gastrin rise. This may have been due to the short duration of treatment, or could imply that suppression alone does not decrease the gastrin response.

T191

## THE EFFECT OF RANITIDINE 150 MG QDS ON 24-H INTRAGASTRIC ACIDITY AND PLASMA GASTRIN CONCENTRATION IN HEALTHY MALE SUBJECTS

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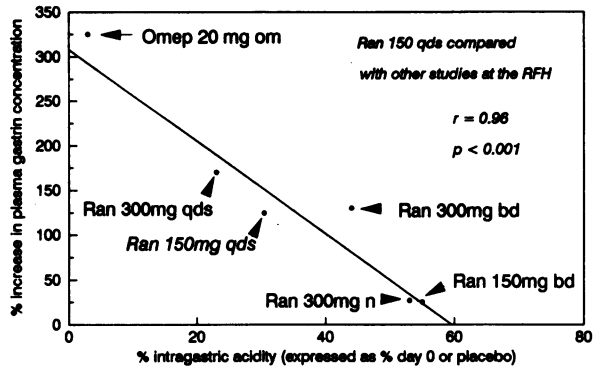
Ranitidine 150mg qds is an effective regimen for the treatment of gastro-oesophageal reflux, but the effect of this dose on 24-h plasma gastrin concentration has not been studied previously.
**Methods:** The 24-h intragastric acidity and plasma gastrin concentrations were measured twice in 23 healthy male subjects. The subjects were studied on the 7th day of dosing with either placebo or ranitidine 150mg qds (after meals and nocte)
**Results: Mean integrated 24h intragastric acidity** (95% CFL): placebo 825mmol.h/L (754-897), ranitidine 150mg qds 265mmol.h/L (212-317); **Mean integrated 24h plasma gastrin:** placebo 410 (306-514;), ranitidine 904 (724-1200) pmol.h/L.




**Conclusion:** Ranitidine 150mg qds suppresses acidity throughout the day and night and increases plasma gastrin concentration. There is a significant inverse correlation between % decrease of acidity and % increase of plasma gastrin concentration.

T190

## LANSOPRAZOLE (LAN) IS MORE EFFECTIVE THAN RANITIDINE (RAN) IN THE HEALING OF GASTRIC ULCER (GU).

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[1]Dundee; [2]Rotherham; [3]Keighley; [4]Paisley; [5]Nottingham; [6]Huddinge; [7]Stockholm; [8]Lederle Laboratories, Gosport.

LAN is a new potent benzimidazole parietal cell $H^+K^+ATP$-ase pump inhibitor; a 30mg daily dose reduces 24 hour gastric acidity by >80%. We assessed if such effective acid inhibition increased the rate of GU healing compared with that achieved by standard dose $H_2$ receptor antagonists (RAN).

Patients with endoscopy proven GU were randomly allocated to receive double-blind treatment with either LAN 30mg or 60mg each morning or RAN 300mg nightly for 4 weeks; therapy was extended to 8 weeks if healing had not occurred earlier. Symptoms were recorded each day on diary cards.

250 patients(17 centres) were recruited. Patients in the 3 treatment groups were well matched for demographic features. Healing (intent-to-treat analysis):

| | LAN 30(n=85) | LAN 60(n=83) | RAN 300(n=82) |
|---|---|---|---|
| Wk 4(% healed) | 78.4* | 83.8** | 60.6 |
| (95% C.I.) | (66.7-86.8) | (72.6-91.0) | (47.9-71.7) |
| Wk 8(% healed) | 98.6*** | 97.3 | 91.4 |
| (95% C.I.) | (90.6-99.9) | (88.9-99.5) | (81.2-96.5) |

LAN resulted in significantly greater healing (*p=0.031,**p=0.003) than RAN at week 4 and a slightly greater healing at week 8(***p=0.063).

Pain relief was rapid and similar in all 3 groups; the proportions pain free were: week 0, LAN 30 20%; LAN 60 18%; RAN 18%; week 4, 70%, 65% and 57% respectively. The median number of days antacids were used for symptom relief were 22%, 20% and 26% respectively. Adverse events(AE) were uncommon and without significant difference between the treatment groups, and none was characteristic of LAN or dose related. The commonest AE (number of patients) on LAN 30, LAN 60 and RAN were: diarrhoea 3,5,3; headache 2,1,5; fatigue and drowsiness 1,3,1 respectively.

In conclusion, lansoprazole is more effective than ranitidine in healing gastric ulcer and is safe; 30mg daily appears to be the optimal dose.

T192

## POLYUNSATURATED FATTY ACIDS, SMOKING AND DUDDENAL ULCER

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Diatary linoleic acid supplementation increases gastric PGE output and depresses gastric acid secretion. The adipose fatty acid profile is said to reflect the pattern of dietary fat intake and in previous studies we found low % adipose linoleic acid in duodenal ulcer patients, suggesting a link between abnormal fatty acid intake, gastric prostaglandin metabolism and duodenal ulcer.

A detailed, prospective dietary history was obtained from 30 duodenal ulcer patients and 26 matched non-ulcer dyspepsia controls with similar weight : height ratios. Fatty acid profiles were measured chromatographically in adipose biopsies taken from each individual.

Mean total dietary fat intake was similar in duodenal ulcer and non-ulcer dyspepsia, 68.8 ± 23 (SD) and 75 ± 27g daily, with a similar fraction as linoleic acid: 10.1 ± 2.8% in duodenal ulcer; 10.1 ± 2.6% in non-ulcer dyspepsia. In contrast adipose % linoleic acid was significantly lower in duodenal ulcer; 7.7 ± 1.85 versus 10.1 ± 2.8%, P<.05. This difference was greatest in smokers; indeed the mean % linoleic acid of the 8 smoking non-ulcer dyspepsia subjects (7.7 ± 1.9) was marginally less than that of the 20 non-smoking duodenal ulcer patients (7.85 ± 1.8).

The adipose fatty acid profile does not reflect dietary intake in duodenal ulcer patients or smokers with non-ulcer dyspepsia. Duodenal ulcer is associated with changes in linoleic acid metabolism, probably depressed cyclo-oxygenase activity, and this abnormality is accentuated by smoking.

T193

ENDOSCOPIC FINDINGS IN SYMPTOMATIC RELAPSE OF DUODENAL ULCER

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Fifty patients with dyspepsia and endoscopically proven duodenal ulcer received an 8 week course of an $H_2$ antagonist. All were shown endoscopically to have healed and treatment was then discontinued. They were followed up for one year and asked to return immediately if there had been recurrence of their presenting symptoms. In all 39 patients relapsed and they were re-endoscoped within 5 days. Only 26 had a recurrence of the duodenal ulcer. Of the other 13 no macroscopic abnormality was found in 10, but 3 had oedema/erythema of the duodenal bulb. All patients had antral infection with H pylori on presentation, healing and recurrence of symptoms. None had a history of NSAID use or previous gastric surgery. There were no differences in the age, duration of symptoms or smoking status between those with and without recurrent ulcer. The 13 symptomatic patients without ulcer recurrence received anti-helicobacter therapy. Ten were rendered helicobacter-free with complete resolution of their symptoms for up to two years of further follow up.

Dyspeptic symptoms within the spectrum of 'duodenal ulcer disease' are not necessarily dependent on the presence of an ulcer crater.

T194

**GASTRODUODENAL pH AND DUODENAL ULCER PAIN.**

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The mechanisms involved in duodenal ulcer (DU) pain production are unclear. We have designed a technique for measuring 24 h ambulatory gastric and duodenal bulb pH to investigate the role of acid in DU pain. Six patients, with endoscopic active DU and daily pain were studied. Combined glass pH electrodes were endoscopically secured in the antrum and first part of duodenum using a clip-fixing device (Olympus HX-2L). Over a 24 hour period ambulatory pH recordings were obtained and the severity of pain charted every 5 minutes. Patients had a median of 12 (range 3-24) episodes of ulcer pain with a median total duration of pain of 200 minutes (55-370). The median duodenal pH during pain was 5.3 (3.1 - 6.8) compared with 5.6 (4 - 6.7) when pain-free ($p < 0.05$). The median intragastric pH during pain was 1.4 (1.1 - 1.7) compared with 2 (1.2 - 3.2) when pain-free ($p < 0.05$).

| | PAIN PERIOD | PAIN-FREE |
|---|---|---|
| % time Duodenal pH>6 | 27(10-80) | 37 (18-84)* |
| % time Duodenal pH<4 | 24(2-63) | 17 (1-51)* |
| % time Gastric pH<4 | 100(80-100) | 74 (63-100)* |
| % time Gastric pH<2 | 92(70-100) | 60 (38-76)* |

*indicates $p < 0.05$ versus pain period

In summary, episodes of DU pain are associated with short periods of lower gastric and duodenal pH suggesting that duodenal acidification plays a role in DU pain production. However, the fact that 27% of pain episodes occurred when duodenal pH was > 6 indicates that other mechanisms such as spasm must also be involved.

T195

MORNING VERSUS EVENING DOSE : A COMPARISON OF 3 H2-RECEPTOR BLOCKERS IN DUODENAL ULCER HEALING.

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The therapeutic efficacy of single nocturnal dose of H2-receptor antagonists has been considered an indirect evidence of the major pathogenic role of nocturnal acid hypersecretion in duodenal ulcer.

In a prospective, single blind, controlled study, 186 patients with endoscopically confirmed duodenal ulcer were randomized and treated for 6 weeks with single doses of cimetidine(C) 800 mg, ranitidine (R) 300 mg, and famotidine (F) 40 mg given either as evening or morning doses.

Endoscopic healing at 6 weeks

| | C | R | F |
|---|---|---|---|
| Morning | 59% | 83% | 93% |
| Evening | 86% | 94% | 97% |

Morning cimetidine is significantly less effective than evening cimetidine regimen in ulcer healing ($P < 0.05$).

Morning therapy with ranitidine and famotidine was comparable to the 3 evening regimens.

Conclusion:

These data may suggest the relative importance of nocturnal over diurnal acid suppression when using cimetidine, an H2-receptor blocker with a short duration of action.

However, this relative importance may be negated by using H2-receptor antagonists with a prolonged action such as ranitidine and famotidine.

T196

NON-STEROIDAL ANTI INFLAMMATORY DRUGS (NSAIDs), GASTRODUODENAL ULCERS AND THEIR COMPLICATIONS: PROSPECTIVE CONTROLLED AUTOPSY STUDY.

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Prospective endoscopic studies demonstrate an association between the use of NSAIDs and the development of gastric and duodenal peptic ulceration. Case-control studies show that the risks of peptic ulcer bleeding and perforation are higher in patients taking NSAIDs than in controls. We have examined the prevalence of peptic ulcers and their complications in a population of 713 patients who died in or outside hospital between January 1990 and October 1991. After verification of drug histories with General Practitioners and hospital records, patients were subdivided prospectively into those taking regular non-aspirin NSAIDs for > 6 months (n=74), irregular or short term NSAID users (n=112), those on aspirin alone (n=63) and controls without a history of NSAID intake (n=464). The stomach and duodenum were opened, washed and examined for ulcers at least 3mm in diameter:

| Patients: | Control (n=464) | Reg NSAID (n=74) | Irregular (n=112) | Aspirin (n=63) |
|---|---|---|---|---|
| Single GU | 13(2.8%) | 5(6.8%) | 7(6.3%) | 2(3.2%) |
| Multiple GU | 10(2.2%) | 1(1.3%) | 9(8.0%) | 4(6.3) |
| GU and DU | 4(0.8%) | 3(4.1%) | 3(2.7%) | 1(1.6%) |
| DU alone | 30(6.4%) | 6(8.1%) | 11(9.8%) | 2(3.2%) |
| Total | 57(12%) | 15(20%) | 30(27%) | 9(14%) |
| Combined GU | 27(5.8%) | | * 35(14%) | |
| Combined total | 57(12%) | | * 54(22%) | |
| Death from bled/perf PU | 12(2.5%) | | # 14(5.6%) | |

* NSAID>controls $p<0.001$, # NSAID>controls $p<0.05$

This study confirms the increased risk of gastric ulcer (but not duodenal ulcer) in users of NSAIDs, and shows that intermittent or short-term use confers no less risk than long-term use. Death from peptic ulcer is commoner in NSAID users than controls.