ROLE OF H. PYLORI INFECTION IN HEALING AND RECURRENCE OF NSAID-ASSOCIATED PEPTIC ULCERS.

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Since the relationship between H. pylori infection and NSAID-related peptic ulcers remains unclear we have evaluated prospectively in a consecutive series of 278 arthritic patients receiving chronic NSAIDs the prevalence of peptic ulcer as well as the effect of H. pylori eradication on the healing and recurrence of gastric and duodenal ulcer found. One hundred peptic ulcers (96 gastric ulcers, 39 duodenal ulcers and 2 gastric ulcers concomitant with a duodenal ulcer) were diagnosed by gastroscopy. Most of these ulcers (70%) were associated with H. pylori infection (diagnosed by histology and rapid urease test). This frequency of infection was significantly inferior (p = 0.01) to that found in 178 patients with minor gastrointestinal lesions (erosions or hyperaemia) or normal endoscopic finding (49%). According to their H. pylori status, ulcer patients were randomized to receive one of the following acute treatments: H. pylori-negative ulcers received omeprazole 20 mg bid for 4-8 weeks, whereas H. pylori-positive ulcers were treated with omeprazole 20 mg bid plus amoxycillin 1 g bid (the latter for the first two weeks) or omeprazole alone for 4-8 weeks whilst continuing NSAID therapy. Endoscopic healing rates for gastric and duodenal ulcers in the three different groups were similar both at 4 and 8 weeks. H. pylori eradication did not influence healing, which occurred in 14/20 (70%) of eradicated patients as compared to 14/17 (82%) in patients with persistent infection. Sixty-one patients with healed ulcer were endoscopically followed-up for 6 months after stopping antibiotic therapy while continuing NSAIDs. Cumulative recurrence rates at 6 months did not statistically differ among the three different groups (27% in H. pylori-negative, 48% in H. pylori-positive and 31% in those eradicated during the acute phase), although a numerical trend in favour of healed cases was evident in infected patients was evident. These findings show that H. pylori eradication does not confer any significant advantage on the healing of NSAID-related gastric and duodenal ulcers in long-term NSAID-users. It remains to be established with certainty whether eradication may be helpful to reduce recurrence in a specific subset of NSAID-associated ulcers.

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MESALAZINE RELEASE FROM COATED TABLETS. EFFECT OF DRUGS WHICH ALTER GASTROINTESTINAL PH. F. Hussen, R. Aljan, N. Trudgill S. Riley. Northern General Hospital, Sheffield, UK.

Euradig S coated mesalazine aims to release its contents in the relatively alkaline environment of the distal ileum and proximal colon. Alkalisation of the proximal gut may lead to premature release of mesalazine with increased risk of systemic toxicity whereas acidification of the gut may leave tablets to pass whole. We have therefore studied the steady state kinetics of coated mesalazine during concurrent administration with omeprazole and lactulose. Six healthy volunteers (3 male, age 17-53) took mesalazine 400mg tds for 21 days. Omeprazole 20mg daily and omeprazole 40mg daily were added from days 8-14 and 15-21 respectively. Urinary and faecal drug excretion were measured on days 7,14,21. Seven constipated but otherwise healthy volunteers (7 female, age 23-37) followed a similar protocol with lactulose 30mls and 60ml daily in place of omeprazole. Stool pH, frequency and whole gut transit time were also measured. During the omeprazole study, median values of N-Acetyl 5ASA (NASASA) and 5-aminosalicylic acid (5ASA) excretions on days 7,14,21 were: 1)alone NASASA: 338, 425, 349; 5ASA 9, 25, 11(mg). 2)faeces NASASA 174, 264, 199; 5ASA 206, 180, 349(mg). During the lactulose alone NASASA 194, 394, 266; 5ASA 8, 14, 9(mg). 2)faecesNASASA 322, 318, 243; 5ASA 134, 239, 162(mg). Lactulose 60mls significantly increased bowel frequency from 2(1)-week to 6 (2-9), but not transit time. 71hrs (52-92) to 58 (42-77) or stool pH 6.6 (5.6-7.5). In addition, neither omeprazole or lactulose (when administered to subjects with constipation) alter the disposition of coated mesalazine.

INCREASED MEASLES IgM IMMUNOREACTIVITY IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE. P. A. Balzola1, A. Khan, A. Pera, F. Bonino, R. E. Pounder, A. J. Wakefield.' Inflammatory Bowel Disease Study Group. Royal Free Hospital School of Medicine, London, UK. "Department of Gastroenterology and Clinical Nutrition, Molinette Hospital, and Division of Gastroenterology, Mauriziano Umberto I Hospital, Torino, Italy.

In an international collaborative study, serum measles IgM immunoreactivity was assayed by ELISA in consecutive outpatients with Crohn's disease (n = 95), ulcerative colitis (n = 79), viral hepatitis (n = 63) and blood donors (n = 30). Results were compared with those obtained from a different commercial measles IgM assay, serum rubella and Epstein-Barr virus-specific IgM immunoreactivity, total serum IgM, Rheumatoid Factor and measles-specific IgG. Twenty patients with inflammatory bowel disease were studied serially over a 4 month period. At the ELISA cut-off point for confirmation of recent acute measles virus infection, there were no significant differences between groups. However, increased serum measles IgM immunoreactivity (> mean ± 2SD of blood donors) was found in patients with Crohn's disease 39/95 (41%) and ulcerative colitis 33/79 (42%) compared with hepatitis patients 5/68 (8%) and normal controls 0/30 (0%) (p<0.001). Those positive by ELISA were also positive by indirect immunofluorescence on the same serum sample. Serum measles IgM immunoreactivity did not correlate with either total IgM, rubella or Epstein-Barr virus IgM (not raised), measles IgG, or disease activity. Patients not receiving steroids were more likely to have raised measles IgM immunoreactivity (p<0.5). All sera examined for Rheumatoid Factor were negative. Of 20 patients with inflammatory bowel disease studied over a 4 month 55% showed raised measles IgM immunoreactivity at some stage during the follow-up. The data suggest an immunological response to measles virus in patients with Crohn's disease and ulcerative colitis, supporting a potential
CIRCULATING SOLUBLE E-SELECTIN LEVELS IN ACTIVE INFLAMMATORY BOWEL DISEASE ARE SIMILAR BETWEEN CROHN’S DISEASE AND ULCERATIVE COLITIS

E-Selectin, one of the members of Selectin family of adhesion molecules, is found only on activated epithelium and plays a major role in inducing slowing and rolling of polymorphonuclear neutrophil granulocytes, by interacting with ligand Sialyl Lewis-x on the granulocyte membrane. We present evidence that soluble E-Selectin (sE-Selectin) levels in the circulation are raised in active inflammatory bowel disease (IBD), and to a similar extent in ulcerative colitis (UC) and Crohn’s disease (CD).

5ml of blood were taken from 11 healthy volunteers, 16 patients with active IBD and 16 patients with inactive IBD. sE-Selectin levels were measured in cell free plasma using an ELISA. The inter- and intra-assay coefficients of variation were less than 5%. To exclude the possibility of cross-reaction with the closely related proteins, L-Selectin and P-Selectin, we tested detergent lysate of peripheral blood mononuclear cells and platelets as abundant sources of these related proteins.

Plasma sE-Selectin in inactive UC and CD [Mean ± SD, 37±21 & 35±13 ng/ml] did not differ from normal [41±14 ng/ml]. However, in both active UC and CD [98±22 & 89±16 ng/ml] there was marked elevation of sE-Selectin.

The disease activity of UC and CD were determined by Crohn’s Disease Activity Index and Truelove & Witts’ criteria respectively. sE-Selectin levels correlated well with disease activity, however, the correlation with inflammatory markers (CRP / ESR) was less significant.

CONCLUSIONS:
1. The elevation of sE-Selectin is significantly suggestive of endothelial activation.
2. There was no significant difference between UC and CD.
3. sE-Selectin is probably shed from activated endothelium and reflects the processes attracting pro-inflammatory cells from the circulation into the mucosa.

QUALITY OF LIFE IN ULCERATIVE COLITIS AND AFTER COLECTOMY WITH ILEO-ANAL-ANASTOMOSIS

Impairment of the Quality of Life (QOL) in patients with Ulcerative Colitis (UC) may be a prominent feature although its assessment is not included in the “activity indices” which are routinely used in the clinical evaluation of the disease. In some cases the impairment of QOL may become one of the main indications to a surgical treatment. Aim of this study was to assess QOL in patients with UC of different severity and patients who underwent proctocolectomy with ileo-anal anastomosis with a J-pouch for severe UC.

Methods: A 29-item questionnaire was developed which dealt with Intestinal Symptoms (IS), Systemic Symptoms (SS), Emotional Function (EF) and Social Function (SF). The questionnaire was previously validated for reproducibility and sensitivity in control subjects and UC patients.

Results were as follows:

<table>
<thead>
<tr>
<th>IS</th>
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<th>EF</th>
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</tr>
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<td>2.7±1.5</td>
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<td>3.5±3.3</td>
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<td>9.5±3.7</td>
</tr>
<tr>
<td>0±0</td>
<td>1.0±1.9</td>
<td>3.1±3.0</td>
<td>6.6±4.6</td>
</tr>
</tbody>
</table>

Mean ± values ± SD: p<0.01 vs remission, p<0.01 vs controls, p<0.01 vs moderate disease.

Conclusions:
1. Patients with UC, even in remission, have a measurable impairment of QOL, which increases with the severity of disease.
2. Operated patients have a QOL which is comparable to patients in remission or with mild disease.
3. In patients with moderate/severe UC proctocolectomy with ileo-anal anastomosis may allow an acceptable QOL.

SMALL INTESTINE TIGHT JUNCTIONS ARE ALTERED IN EXPERIMENTAL COLITIS IN THE RAT

Intestinal permeability is often altered in Inflammatory Bowel Diseases (IBD) but its relationship with the localization and degree of inflammation is still not well understood. Aim of the study was to evaluate the effects of acute inflammation of the distal colon on the morphology of the Tight Junctions (TJs) of the duodenum and distal ileum. Methods: Colitis was induced in 9 male Sprague-Dawley rats (body weight 200 - 250 g) by intracolonic administration of trinitrobenzenesulphonic acid (25 mg in 50 % ethanol). 4 rats served as Controls (C). After 1 week the rats with colitis were divided in one group with severe colitis (SC, n=4), defined by the presence of diarrhea, weight loss and a macroscopic lesion score of > 5 and one group with mild colitis (MC, n=5), characterized by absence of diarrhea, weight loss and a lesion score < 4. The morphology of the TJs was assessed in the duodenum and the terminal ileum with Transmission Electron Microscopy after ex vivo perfusion of the intestine with 4 % lanthanum nitrate via the abdominal aorta. The degree of penetration of the marker into the junctional complexes was taken as a measure of the TJs disruption. To assess also transepithelial permeability, in an additional experiment (SC: n = 4; C: n = 3) we measured the duodenal absorption of 3H-mannitol (3H(α-Dmannitol) instilled with a closed loop technique after ligation of the renal arteries. After 2 hours the animals were sacrificed and radioactivity was determined in serum. Satistics: unpaired t-test.

Results: Controls vs mild colitis vs severe colitis

colon wet weight: mg 1590 ± 66 2733 ± 1021 5347 ± 1056
% open TJ’s: duodenum 64 ± 2.0 59.7 ± 4.5** 84.4 ± 4.1** ileum 83.2 ± 6.0 60.2 ± 7.0** 85.0 ± 1.5**
H2-mannitol uptake; dpm 4609 ± 450 n.d. 3984 ± 305 ± 1.0

mean data ± SEM; n.d. = not determined; *p<0.05, **p<0.01 or less vs C.

Conclusions: 1) Intestinal segments proximal to inflamed colon showed significant alterations of the TJs. 2) The degree of these alterations is related to the degree of inflammation. 3) These alterations may allow the entry of luminal antigens into the mucosa and have a pathophysiologic role in inflammation and 4) the alteration of transcellular absorption may contribute to the pathogenesis of diarrhea.

AGONIST-EVOKED INCREASES IN INTRACELLULAR CALCIUM IN HUMAN COLONIC CRYPTS

Background/Aims: The secretory response of the human colon is altered in disease states (diarrhoea, constipation). Intracellular calcium [Ca2+] shows a strong stimulatory action on most intestinal functions. It has been implicated as a mediator of colonic secretion. The study aimed to (i) isolate functionally viable colonic crypts (ii) measure [Ca2+] using microfluorometry techniques, with the fluorescent calcium indicator, fura-2.

Methods: Human colonic tissue was obtained from surgically resected specimens. These procedures were approved by the Ethical Committee. Colonic crypts were dissociated using 200U collagenase in Ca2+-free Hanks balanced salt solution. Isolated crypts were fixed with Cell-Tak coated coverglass then loaded with 1μM fura-2AM (for 20mins at 37°C). Basal levels of [Ca2+], were determined using the calcium ionophore ionomycin (10μM) and 10nM MgCl2. Individual crypts were exposed to a sustained application of the purinoreceptor agonist ATP (30μM, 500μM, 5mM), known to evoke an increase in [Ca2+].

Results: Estimated basal levels of [Ca2+], were 345.2±41.5 ng (n=7)

The responses with all three concentrations of ATP were transient in nature. The amplitudes of the [Ca2+], increases were not dependent upon the concentration of ATP. 30μM ATP elevated [Ca2+] by approximately 52nM (n=7) above basal [Ca2+], 500μM ATP 130nM (n=5), and 5mM ATP 31nM (n=2).

Conclusion: This preliminary study is the first to report estimations of [Ca2+], in isolated human colon crypts, and may provide the methodology to study the role of [Ca2+] in diseased states of the human colon.
Expression of endothelial adhesion molecules in colorectal neoplasia

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Intercellular adhesion molecule-1 (ICAM-1), intercellular adhesion molecule-3 (ICAM-3), vascular cell adhesion molecule-1 (VCAM-1) and endothelial cell adhesion molecule-1 (ELAM-1) or E-selectin are inducible endothelial surface molecules involved in leucocyte adhesion. These molecules may also have an important role in the process of tumour metastasis, through their interaction with tumour cells. We examined the expression of these adhesion molecules in the endothelium of 46 colorectal carcinomas, 13 adenomas and in normal colorectal mucosa in frozen tissue sections. ICAM-1 was strongly expressed in the endothelial cells of both small arteries and veins in all normal and neoplastic cases. VCAM-1 showed a variable expression, with focal strong positivity in arteries and mild to moderate staining in most of the small veins in all carcinoma cases, and only mild staining in adenomas and in the endothelium of normal mucosa. E-selectin and ICAM-3 were not expressed by normal mucosa vessels, but while all carcinomas and 11/13 adenomas showed staining in the small venules with E-selectin, ICAM-3 was positive in the endothelium of only 3/46 carcinomas. Our findings suggest that colonic neoplasia induces a variable upregulation of the expression of endothelial adhesion molecules. This upregulation is probably a result of cytokine stimulation and may affect the host inflammatory response to the tumour, as well as the metastatic process.

The correlation between anal sphincter defects and pressure profiles. Benson M*.

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To study the relationship between ultrasonographic sphincter defects and pressure profiles we investigated 115 patients with faecal incontinence. Endoanal ultrasound was performed using a rotating 7.5 MHz probe and the anal pressure profile was obtained using a water-filled microballoon system. 63 of the 115 (55.8%) patients had a demonstrable sphincter defect. There was no significant difference in the mean ages of these patients (55.2 (2.6) vs 55.5 (2.4)). 8 patients had an internal anal sphincter (IAS) defect, 30 patients had an external sphincter (EAS) defect and 28 patients had a defect in both the IAS as well as the EAS. There was no significant difference in the mean basal pressures (cm H2O) in the sphincter defect and no sphincter defect groups [63.6 (4.9) vs 61.2 (3.5), p > 0.05]. Similarly there was no significant difference in the squeeze pressures between the two groups [126.7 (9.5) vs 107.8 (5.9), p > 0.05]. When the site of the defect was taken into account, there was no significant difference in the basal pressures regardless of whether the defect was in the IAS, EAS or both. However, the squeeze pressure was significantly lower pressure in the group with an EAS defect (p < 0.05). Squeeze pressures in the group with IAS defects and combined defects were not significantly different from those with no defect. These data show that sphincter pressures are a poor indicator of the morphological integrity of the anal sphincter complex.
IBD and colorectal

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