DO PHARMACOLOGICAL AGENTS FOR PORTAL HYPERTENSION COMPROMISE RENAL FLOW?

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Both propranolol (PROP) and isosorbide-5-mononitrate (ISM0) are commonly used in the management of portal hypertension. Recently, concern has been expressed that these drugs may compromise renal function in cirrhotic patients by reducing renal perfusion as a result of their hypotensive action. We assessed the haemodynamic effects including renal blood flow of these drugs.

Methods: 12 cirrhotic patients were studied. After an overnight fast, heart rate (HR), mean arterial pressure (MAP), hepatic venous pressure gradient (HPVG), azysogous flow (AZY) and unilateral renal vein flow (RBF) (by direct reverse thermistor method) were recorded. Patients were then treated with PROP (6 patients, mean Chilad-Pugh score (CPS) 5.2 (1.3)) or low dose ISM0 (6 patients, mean CPS 9.7 (1.7)) and the above measurements repeated after 60 minutes.

Results: There was no correlation between the baseline RBF and CPS although it was significantly reduced in patients with severe ascites (p<0.01). Haemodynamic parameters at baseline (pre) and at 60 minutes (post) are summarised below:

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<thead>
<tr>
<th></th>
<th>PROP</th>
<th>ISMO</th>
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<tbody>
<tr>
<td>HR</td>
<td>80.3(5.1)</td>
<td>87.7(8.3)</td>
</tr>
<tr>
<td>MAP</td>
<td>80.5(4.9)</td>
<td>87.4(6.2)</td>
</tr>
<tr>
<td>HVPG</td>
<td>18.8(2.7)</td>
<td>11.0(1.4)</td>
</tr>
<tr>
<td>AZY</td>
<td>483.1(30.1)</td>
<td>614.2(26.9)</td>
</tr>
<tr>
<td>RBF</td>
<td>543.8(9.9)</td>
<td>265.2(53.9)</td>
</tr>
</tbody>
</table>

Results are expressed as mean (standard error) with pressures in mmHg and flow in ml/min. (p>0.05, *p<0.01, **p<0.001)

Conclusions: Despite the anticipated reduction in other haemodynamic parameters, RBF did not fall significantly following administration of either PROP or ISM0 to cirrhotic patients.

IBD and colorectal F228-F238

INCREASED EXPRESSION OF CIRCULATING LEUCOCYTE ADHESION MOLECULES CD11b AND CD18 IN INFLAMMATORY BOWEL DISEASE. CE Collins, C Davies, MO Macey*, DA McCarthy*, DS Rampton. GI Science Research Unit and Department of Haematology*, St Bartholomew’s and The Royal London School of Medicine and Dentistry, Whitechapel, London.

Adhesion of leucocytes to vascular endothelium depends in part on their expression of specific surface antigens. Among these, CD11 and CD18 bind to endothelial cell intercellular adhesion molecules-1 and -2. Leucocyte activation is a feature of inflammatory bowel disease (IBD) and monocyte-endothelial cell interaction may be an early event in pathogenesis. Conventional therapy including sulphasalazine may reduce expression of leucocyte adhesion molecules. We tested the hypothesis that IBD is associated with up-regulation of circulating leucocyte adhesion molecules.

METHODS: Using fluorescently-labelled specific monoclonal antibodies and a novel flow-cytometric method, we measured leucocyte surface expression of the antigens CD11a, b and c and CD18 in unixed whole blood in Crohn’s disease (CD), ulcerative colitis (UC) and healthy controls.

RESULTS: No statistically significant changes in % cells positive for these antigens were detected, but for CD11b and CD18, mean fluorescence intensity (MFI), a quantitative measure of antigen density, was increased for granulocytes (GNNs) and monocytes (MNs) in IBD.

MFI expressed as median (interquartile range):

<table>
<thead>
<tr>
<th></th>
<th>GNNs</th>
<th>MNs</th>
</tr>
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<tbody>
<tr>
<td>CD11b</td>
<td>30 (26-34)</td>
<td>27 (22-38)</td>
</tr>
<tr>
<td>CD18</td>
<td>40 (39-41)</td>
<td>82 (86-92)</td>
</tr>
<tr>
<td>healthy controls</td>
<td>10</td>
<td>91</td>
</tr>
<tr>
<td>active CD</td>
<td>10</td>
<td>97</td>
</tr>
<tr>
<td>inactive CD</td>
<td>11</td>
<td>71</td>
</tr>
<tr>
<td>active UC</td>
<td>11</td>
<td>69</td>
</tr>
<tr>
<td>inactive UC</td>
<td>9</td>
<td>80</td>
</tr>
</tbody>
</table>

CONCLUSIONS: Increased expression of the adhesion molecules, CD11b and CD18, on circulating granulocytes and monocytes is likely, by enhancing leucocyte adhesion to vascular endothelium, to promote cellular diapedesis and infiltration of the bowel wall in IBD.
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INCREASED INDUCIBLE CYCLOOXYGENASE ASSOCIATED WITH TREATMENT FAILURE IN ULcerATIVE COLITIS

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INTRODUCTION: The cyclooxygenases (COX)-2 gene is induced at sites of inflammation and in colonic carcinomas and normally suppressed by steroids. Since COX-2 could be important for malignant change or prostaglandin dependent secretion in ulcerative colitis, we investigated COX-2 expression in colonoscopic mucosal samples from patients with ulcerative colitis, and normal controls, and related results to expression of inducible nitric oxide synthase (iNOS) and interleukin (IL)-8 since these are normally co-induced.

METHODS: Mucosal biopsy samples were obtained from 17 patients with ulcerative colitis (8 surgery, failed steroid therapy), 9 newly diagnosed, and 10 active disease. RNA extraction (RNAzol) and reverse transcription, polymerase chain reaction (PCR) amplification of specific cDNA sequences for COX-2 (232 base pairs, 23 cycles), iNOS (453 base pairs, 28 cycles), IL-8 (220 base pairs, 23 cycles) and GAPDH (reference housekeeping gene, 650 base pairs, 23 cycles) was carried out and PCR product assayed using a semia quantitative enzyme linked gonadosectedel immunoluluminometric assay.

RESULTS: PCR product levels (median and IQR) expressed as proportion of GAPDH (x10) for COX-2 are shown in the table.

CONCLUSION: COX-2 expression is increased in inflammatory bowel disease (IBD) and may be a marker for both acute and persistent disease.

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IMAGING OF E-SELECTIN, A SPECIFIC MARKER OF ENDOTHELIAL CELL ACTIVATION, IN THE EVALUATION OF INFLAMMATORY BOWEL DISEASE.

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E-Selectin expression is up-regulated in response to pro-inflammatory cytokines and makes an integral part of the process leading to accumulation of inflammatory cells in the tissue. Tissue E-Selectin expression is increased in inflammatory bowel disease (IBD) and we have investigated its potential for targeting the inflammatory activity in IBD.

METHODS: 9 Ulcerative colitis (UC) and 7 Crohn’s disease (CD) patients with varying degrees of active inflammation were selected with prior consent. Following intravenous administration of 111-Indium (111-In) labelled antibody to E-Selectin, anterior, posterior and lateral images were obtained 4hrs, 24hrs and 48hrs post injection by gamma camera equipped with medium-energy general-purpose collimator. A 99-Technetium (99-Tc) labelled scan was performed the following day.

RESULTS: 9 out of 16 patients had active areas of inflammation, defined by 99-Tc labelled white cell scans. The extent of inflammation demonstrated by 111-In labelled E-Selectin scan ranged from par-colitis in active UC to localised areas of inflammation both in UC and CD. 10 patients with active IBD had positive E-Selectin scans. The results were concordant in 9 and discordant in 3. Four patients were negative on both types of scan.

CONCLUSIONS: We have demonstrated that E-Selectin scan can localise the area of inflammation through the process which is simpler than white cell scan. It is more versatile and can be done in neutrophilic patients.

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PROGNOSTIC VALUE OF WHOLE GUT LAVAGE FLUID ANALYSIS IN CROHN’S DISEASE.

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There are no reliable methods to determine the probability of relapse in Crohn’s disease. Though prognostic indices based on ESR, CRP and C-reactive protein have been designed to predict outcome, serum proteins poorly reflect mucosal immune events, and such indices have not generally been found useful. Analysis of whole gut lavage fluid (WGLF) is an objective measure of activity of IBD, and gut immune events such as neutrophil migration and proinflammatory cytokine production can be investigated. The aim of this study was to investigate whether WGLF parameters are of prognostic relevance with respect to relapses of disease. Thirty patients with Crohn’s disease were in remission (no symptoms, normal ESR, CRP, white cell count, WGLF IgG ≤ 10µg/ml) at the time of whole gut lavage with polyethylene glycol electrolyte (Kleen-Prep) solution. Granulocyte elastase (GE), a marker of neutrophils in WGLF was assayed using a highly specific substrate, L-prolyl-L-prolyl-L-valine-p-nitroanilide (Quadratech, UK). IL-1β in WGLF was assayed using a commercial ELISA kit (Glaxon, USA).

Two patients had detectable GE in WGLF, and 10 of them were not in remission at 1 year after the initial lavage; 4 had a relapsing course (needing steroid therapy), 5 were steroid dependent and 1 was on immunosuppressive therapy. In contrast, 18 patients in remission had undetectable GE in WGLF, and 12 of them were in remission at 1 year needing no therapeutic intervention (p<0.01). Ten of the patients in remission had detectable IL-1β in WGLF and 8 of them were not in remission at 1 year after the initial lavage; 3 had a relapsing course (needing steroid therapy), 4 were steroid dependent and 1 was on immunosuppressive therapy. In contrast, 19 patients had undetectable IL-1β in WGLF, and 12 of them were in remission at 1 year needing no therapeutic intervention (p<0.01).

In conclusion, in Crohn’s disease patients in remission, detectable GE or IL-1β in WGLF is associated with a poorer outcome at 1 year.

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IN SITU IMMUNE RESPONSES IN CROHN’S DISEASE: A COMPARISON WITH ACUTE AND PERSISTENT MEASLES VIRUS INFECTION.

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The implied aetiological association of measles virus with Crohn’s disease would be supported by detection of an immune response to infected cells in affected tissues. This study sought to detect and characterise in situ immune responses to measles virus in both acute and persistently infected tissues, and in particular, Crohn’s granuloma. Serial tissue sections from cases of Crohn’s disease (n = 17), measles (n = 9), acute infectious mononucleosis (n = 5), acute measles pneumonitis (n = 2), acute measles appendicitis (n = 1), subacute sclerosing panencephalitis (SSPE; n = 1), and measles inclusion body encephalitis (MIBE; n = 1), were examined. Single and double immunohistochemical labelling was performed to identify both cytotoxic lymphocytes (CD8, TIA) and perforin, CD45RO, CD45RA macrophages (KP1).

The relationship of these cells to measles infected cells was identified by double immunolabelling with anti-measles virus nucleoprotein antibody. In both acute measles appendicitis and SSPE, CD8+ / TIA+ cytotoxic lymphocytes (CTL) targeted infected cells. In the other tissues that were positive for measles virus infection including Crohn’s disease (13/17) - where staining was largely confined to granuloma, MIBE, fatal pneumonitis, and tuberculosis granulomata, infected cells appeared to be targeted by macrophages rather than CTL. The CTL in Crohn’s granuloma were Leu 7 and perforin /CD45RO (naive). CTL in both tuberculosis and Crohn’s granulomata were similar in their peripheral distribution, number and phenotype. The data suggest that measles-specific CTL responses may be attenuated in Crohn’s disease compared with acute measles appendicitis and SSPE, and secondly, that an abnormal macrophage response to persistent measles virus infection of the intestine may result in granulomatous inflammation.
DOSE LOADING WITH ORAL MESALAZINE: OPTIMISING DRUG CONCENTRATIONS IN THE MUCOSA F. Husain, R Ajan, N Trugill, S Riley. Dept of Gastroenterology, Northern General Hospital, Sheffield, U.K.

Mesalazine based products are widely used in the maintenance of ulcerative colitis remission. However, the optimal dose remains unknown since dose-ranging studies have yielded conflicting results.

We have therefore studied steady-state kinetics and mucosal drug levels in healthy volunteers taking progressively larger doses of oral mesalazine. 12 subjects (7 male, aged 18-30), were given delayed release mesalazine 400mg tds for 7 days. Serial blood and rectal mucosal samples and urine and stool were collected over 24 hours. Following a drug free interval the same subjects repeated the protocol with 800mg tds and 1600mg tds. Samples were analysed for 5-aminosalicylic acid (SASA) and N-acetyl-5-ASA (NA5ASA) by HPLC. Median results are shown below (NA5ASA/SASA).

<table>
<thead>
<tr>
<th>Plasma/oral (mg/ml/mg)</th>
<th>Urine (mg/mg)</th>
<th>Faeces (mg/mg)</th>
</tr>
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<tbody>
<tr>
<td>400 tds 17.2/3.9</td>
<td>249.8/1.8</td>
<td>261.9/124</td>
</tr>
<tr>
<td>800 tds 30.9/15.4</td>
<td>523.7/85.5</td>
<td>242.7/024</td>
</tr>
<tr>
<td>1600 tds 56.8/46.8</td>
<td>1468.4/44.6</td>
<td>269.7/14</td>
</tr>
</tbody>
</table>

(AUC=area under curve).

Following serial dose-doubling with oral mesalazine i) Combined faecal and urinary excretion (SASA+NA5ASA) increases proportionally. ii) Urinary excretion (SASA+NA5ASA) progressively exceeds faecal excretion. iii) The proportion of 5ASA to NA5ASA increases indicating saturation in urine, plasma, stool and rectal mucosa. iv) At higher dose, the increase in rectal mucosal levels is modest in comparison with the increase in plasma concentration and urinary excretion.

PSYCHOLOGICAL MORBIDITY IN INFLAMMATORY BOWEL DISEASE: THE IMPACT OF A COUNSELLING SERVICE
Smith GD, Luman W, Roger D, Palmer KR. Gastrointestinal Unit, Western General Hospital, Edinburgh.

It is often assumed that counselling may alleviate many of the psychological problems associated with Crohn’s disease (CD) and ulcerative colitis (UC) although this has not been proven.

Fifty patients with CD (38 females, median age 38), 50 UC patients (22 females, median age 38) and a group of 50 healthy volunteers (HV,27 females, median age 34) underwent structured interviews and completed a range of questionnaires measuring several facets of psychological wellbeing (Hospital Anxiety and Depression Score, HAD, Attitudes & Preferences, Style and Strategies, questionnaire). Patients with CD and UC were then randomised to receive either a counselling package or routine clinical follow-up. The counselling package consisted of diverse specific educational videos, information booklets and the teaching of stress management techniques.

Patients were reassessed at six months.

At baseline, the scores for HAD, SS and AP were within the normal range in patients with UC and HV. CD patients had higher anxiety level than HV (mean anxiety score CD 10.1, UC 7.7, HV 6.8, p<0.001). CD patients also demonstrated significant maladaptive coping mechanism on SS score (mean maladaptive score CD 19.1, UC 15, HV 12, p<0.001). At follow-up, the anxiety score of counselled CD patients improved significantly (p<0.05) as did their maladaptive coping mechanism (p<0.005).

Psychological morbidity is common in CD and can be quantified using validated questionnaires. These aspects of psychological morbidity can be effectively treated by specific counselling.

A COMPARATIVE STUDY TO INVESTIGATE FACTORS ASSOCIATED WITH IRRREGULARITIES OF BOWEL FUNCTION AMONG HEALTHY BENGALIS IN CALCUTTA AND SHEFFIELD AND ENGLISH SUBJECTS IN SHEFFIELD S. SENGUPTA, N.W. READ, CENTRE FOR HUMAN NUTRITION, NORTHERN GENERAL HOSPITAL, SHEFFIELD S5 1AU, U.K.

INTRODUCTION Factors underlying irregular bowel habits (IBH) are unknown but previous studies have implicated gender and diet. These may vary in different cultural and ethnic groups in the UK, e.g., that more females than males (2:1) have Irritable bowel syndrome (IBS) while in India, it seems that more males than females (3:1) have IBS. This study was designed to investigate the incidence of IBH in the general population in India and UK and explore how patterns of bowel habit are related to different cultural background, gender, psychological factors and patterns of eating and other behaviours.

METHODS A questionnaire on bowel habits, eating behaviour, mood and other behaviours was completed by 318 Bengalis in Calcutta (156 M and 159 F) and 108 Bengalis in Sheffield (51 M and 57 F) and 233 English in Sheffield (101 M and 132 F).

RESULTS 52.7% of Bengalis in Calcutta reported IBH compared with 53.4% Bengalis and 49.8% English in Sheffield. IBH was more common in female English subjects in UK (m/f; 39:77) and in male Bengalis in Sheffield (m/f; 32:17) and Calcutta (m/f; 97:69). A greater percentage of Bengalis and English with IBH than those with regular bowel habit (RBH) reported inconsistent meal times, frequent snacking, breakfast skipping, frequent micturition, and sleep disturbance. None of these could account for the gender specificity of bowel habit within the three populations. Other factors were common in Bengalis with IBH which could account for male preponderance were consumption of tea, coffee, alcohol and beer, leafy vegetables and meat consumption. 72% of male Bengalis in Calcutta and 63% of male Bengalis in Sheffield with IBH were married compared with only 44% Bengali males in Calcutta and 26% Bengali males in Sheffield with RBH. Frequent mood change (FMC) was also more common in IBH subjects from all three groups and showed a female predominance among the English subjects and a male predominance among the Bengalis in Sheffield and Calcutta.

CONCLUSION An association between IBH and irregulations of several different behaviours and mood was observed in all three groups, though the data suggest that changes in dietary elements and alcohol consumption and FMC are all associated with the male predominance within the Bengalis with IBH.
Small intestine and diarrhoea


The incidence of diarrhoea in the small intestine is uncertain. This study was undertaken to assess the prevalence of diarrhoea in a group of patients with gastrointestinal symptoms.

Patients: A total of 100 patients, 50 male and 50 female, were studied. The age range was 18 to 78 years (mean 45 years).

Methods: A questionnaire was used to assess the presence of diarrhoea in the past year. The incidence of diarrhoea was calculated using the formula:

\[
\text{Incidence} = \frac{\text{Number of patients with diarrhoea}}{\text{Total number of patients}} \times 100
\]

Results: The incidence of diarrhoea in the past year was 30% in the male group and 28% in the female group.

Conclusion: The incidence of diarrhoea in this group of patients is similar to that reported in other studies.

Detection of faecal incontinence


Faecal incontinence is a common complaint in patients with gastrointestinal symptoms. The present study was undertaken to assess the incidence of faecal incontinence in a group of patients with gastrointestinal symptoms.

Patients: A total of 100 patients, 50 male and 50 female, were studied. The age range was 18 to 78 years (mean 45 years).

Methods: A questionnaire was used to assess the presence of faecal incontinence in the past year. The incidence of faecal incontinence was calculated using the formula:

\[
\text{Incidence} = \frac{\text{Number of patients with faecal incontinence}}{\text{Total number of patients}} \times 100
\]

Results: The incidence of faecal incontinence in the past year was 15% in the male group and 12% in the female group.

Conclusion: The incidence of faecal incontinence in this group of patients is similar to that reported in other studies.