Dyspepsia, *H. pylori* and bleeding  W1-W17

**DYSPEPSIA WORKLOAD IN PRIMARY CARE**

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Background: Dyspepsia (symptoms referable to the proximal alimentary tract) accounts for 5% of workload in primary care, yet relatively little is known about the characteristics of patients who consult with dyspepsia symptoms. Data relating to case mix is vital pre-requisites for the development of clinical guidelines which are responsive to the needs of GPs, and will allow targeting of specialist advice and resources to relevant patient sub-groups.

Methods: Data was collected on consecutive patients consulting GPs at 3 multi-partner practices, with a total target population of 22,549. Demographic data, and details of symptoms, recent drug therapy, and past investigations were recorded prospectively. We report data from the first 400 consultations, relating to 220 individual patients.

Results: Demographics: Mean age (SD): 54 (17). 32% under 45 years; M : F; 114:106. Symptoms: see Table; 20 (9%) had ‘unsure symptoms. Investigations: see Table; previously investigated: 131 (60%); >1 test: 25 (11%).

(mean) (range) were: 6 years ago (range: 0–40 yrs). Recent therapy: see Table; 30% (14%) taking antacids already. 103% (38%) taking acid-suppressing drugs.

**Table:**

<table>
<thead>
<tr>
<th>Group</th>
<th>Total patients</th>
<th>Uninvestigated patients</th>
<th>- never consulted before</th>
<th>- consulted in the past</th>
<th>Normal / minor finding</th>
<th>- Reflux oesophagitis (RO)</th>
<th>- Peptic ulcer (PU)</th>
<th>- Both RO and PU</th>
<th>Recent NSAID%</th>
<th>Recent ASD%</th>
</tr>
</thead>
<tbody>
<tr>
<td>EP</td>
<td>220</td>
<td>41.8</td>
<td>35</td>
<td>23.2</td>
<td>12.7</td>
<td>37.7</td>
<td>38.2</td>
<td>24.7</td>
<td>1.1</td>
<td>5.0</td>
</tr>
<tr>
<td>HR</td>
<td></td>
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</tbody>
</table>

**Symptoms:**

- EP- = Epigastric pain, HP = Heartburn & regurgitation, Mixed-EP and HP. Pre-endoscopy 1.1.6 ± 0.08, 1.5 ± 0.08 0.67

**Other findings:**

- Disability, visits and medications used. There were 145 positive patients (56%) who had had no endoscopy previously. Most patients were referred on the basis of positive test results, with a fifth of patients referred for medical management.

**Summary:**

There was no difference in symptoms, disability, GP visits or prescription between groups. There was a trend for the endoscoped group to consult more frequently. There were no significant differences between the groups during follow-up.

**Conclusions:**

- It is safe to manage young H. pylori negative dyspeptic patients without endoscopy.

**CURRENT USE OF HELICOBACTER SEROLOGY FOR PRE-ENDOSCOPY SCREENING IN THE UK**

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Considerable savings have been reported using Helicobacter pylori (HP) serology as a pre-endoscopy screening test for young dyspepsics although the extent of these savings and the efficacy of various clinical strategies have been disputed. We conducted a survey amongst UK hospital gastroenterologists and general practitioners with an interest in gastroenterology to establish current practice in the management of dyspepsia under the age of 45 years.

Postal questionnaires were sent to 536 members of the British Society of Gastroenterology and 164 members of the Primary Care Society in Gastroenterology in November 1995. The response rate was 58%.

HP serology is currently used by 25% of general practitioners and 17% of gastroenterologists. Following screening, most general practitioners would eradicate infection prior to endoscopy (92.4%) whilst most gastroenterologists (74.5%) would endoscopy patients before treatment. 70% of gastroenterologists would endoscopy sero-positives. Of those not currently using serology, 78% would use it as a pre-endoscopy test if it was available. 106 different drug regimens were used by respondents as first line HP treatment. 83.4% used triple therapy and the most popular combination was that of omeprazole, amoxicillin and metronidazole (38.2%). Following treatment 57% of respondents re-tested selected patients, 29% re-tested all patients and 14% never re-tested.

Our survey shows that in the UK, HP serology is currently used as a pre-endoscopy screening test for young dyspepsics by only a fifth of gastroenterologists. There is a wide variation in strategies preferred by hospital gastroenterologists and by general practitioners. Trials comparing symptomatic outcome and economic consequences of different HP serology based clinical strategies are needed.

**CUT-OFF POINT FOR 13C-UREA BREATH TEST**

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The 13C-urea breath test (UBT) is now widely used as a non-invasive test to detect the presence of *H. pylori*. Based on an earlier comparative study of 165 patients, a cut-off point of 5.0 13C excess at 30 minutes post urea has been used to discriminate between positive and negative tests.

The aim was to use data from clinical trial and routine practice to see if the cut-off point was correctly set at 5.0.

Results from 950 visits of 354 patients entered into placebo controlled clinical trials of *H. pylori* eradication therapy have been examined. Culture, histology and standard UBTs were carried out at baseline, 4 weeks, 6 months and 12 months post treatment. Test performance was compared against a gold standard of the majority result. A cut off of 3.5 gave a sensitivity of 98.5 and specificity of 97.0 compared with a sensitivity of 96.8 and specificity of 99.3 using a cut-off of 5.0.

In 935 routine UBTs carried out at a single centre, to detect the presence of *H. pylori* in patients and to assess the success of *H. pylori* eradication therapy, 13C excess was > 3.5 in 615 tests, in 11 tests the excess was between 3.5 and 5 and 300 > 5.0. Based on clinical findings the cut off value of 5.0 gave false negative results in these tests. There was no significant difference between the excess for the negative tests in untreated and treated patients (mean ± SD 1.1 ± 0.5 v 1.1 ± 0.6).

Receiver Operator Curves were constructed for trial data, routine data and combined data, which indicated that the correct cut-off was 3.5.

Both clinical trial data and routine use of the UBT support the conclusion that the cut-off point for 13C should be lowered from 5.0 to 3.5.
GASTRIC MUCOSAL CYTOKINE GENE EXPRESSION (CGE) IN H. PYLORI (HP) AND DUODENAL ULCER (DU) DISEASE
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Department of Medicine, Clinical Sciences Centre, Northern General Hospital, Sheffield S5 7AU, 1Department of Pathology and *Gastroenterology, Rotherham District General Hospital, S60 2UD.

Introduction Cytokines mediate inflammation and may be involved in the development of gastritis and ulcer disease. Aim Pilot study to compare CGE in non-ulcer patients (1) without and (2) with infection vs. (3) DU. Methods 1) Biopsies taken from antrum and DU edge. 2) IL-1α, IL-1ß, IL-2, IL-4, IL-6, IL-8, IL-10, IL-13, IFNγ and TNFα gene expression detected by reverse transcription-polymerase chain reaction.

Results Patients (pts) n= CGE (type and in number of pts) 1) Hp*non-DU(control) 6 1) IL-8: 1/6 2) Hp* non-DU 7 2) IL-1ß: 1/7, IL-8: 3/7. 3) Active DU (all Hp*) 7 3) Antrum: IL-1ß: 5/7, IL-6: 2/7. IL-8: 6/7, TNFα: 1/7. 4) DU edge: IL-6: 4/4, IL-8: 4/4.

Other cytokines were not detected. There was little CGE in the dyspeptic pts without HP infection. The presence of the organism was associated with some increase in IL-8 expression frequency. However, the CGE profile widened when DU was present with antral IL-1ß and IL-8 expressed in most IL-6 and IL-8 at the ulcer edge in all.

Discussion The high frequency of IL-1ß, IL-6 and IL-8 mRNA expression in active DU, over and above that seen in HP infection alone, suggest they may be involved in ulcer formation. Alternatively, non-ulcer and ulcer-associated HP strains may cause different patterns of CGE, possibly independent of ulcerogenesis itself.

Conclusion These early data are consistent with cytokine involvement in DU disease, perhaps causally.
ERADICATING H. PYLORI REDUCES HYPERGASTRINAEMIA ASSOCIATED WITH LONGTERM OMEPRAZOLE THERAPY. A.M. EL-Nimi, J.E.S. Ardill, K.E.L. McColl, University Department of Medicine and Therapeutics, Western Infirmary, Glasgow, Scotland.

In man, acid inhibition by proton pump inhibitors results in hypergastrinaemia. In some longer term animal studies this hypergastrinaemia has led to ECL-cell hyperplasia and carcinoid tumours. Helicobacter pylori infection also causes hypergastrinaemia and is frequently present in patients prescribed anti-secretory therapy. We have assessed the value of eradicating H. pylori as a means of reducing omeprazole-induced hypergastrinaemia in man.

Twenty H. pylori positive patients with oesophagitis or peptic ulceration were randomised to receive two weeks treatment with either symptomatic therapy or triple H. pylori eradication therapy (De-Nol, Metronidazole and Amoxicillin). H. pylori status was reassessed 4 weeks later by 14C urea breath and then all subjects were commenced on omeprazole 40mg/day for 4 weeks followed by 20mg/day for 6 months. Basal serum gastrin concentrations were measured on entry, 4 weeks following HP eradication/symptomatic therapy and after 1 & 7 months of omeprazole therapy.

<table>
<thead>
<tr>
<th>Medium (range) Basal Gastrin Results (pg/ml)</th>
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<tbody>
<tr>
<td>Initial assessment</td>
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<tr>
<td>Patients randomized to H.P erad.</td>
</tr>
<tr>
<td>54</td>
</tr>
<tr>
<td>38</td>
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</table>

* Higher than value on initial presentation at p<0.01.

The gastrin-lowering effect of eradicating H. pylori infection completely counteracted the gastrin-elevating effect of the proton pump inhibitor.

Conclusion: These findings support a policy of eradicating H. pylori infection in patients requiring longterm proton pump inhibitor therapy. This research was supported by Astra Pharmaceuticals.

THE EQUILIBRIUM BETWEEN H. PYLORI COLONISATION DENSITY AND GASTRIC ACID SECRETORY CAPACITY IN DUODENAL ULCER AND NON-ULCER SUBJECTS PD Mullin, P Sarfie1, D Fine, HW Steer2, Departments of Medicine, Pathology, Surgery. Southampton University Hospitals, Southampton UK.

Introduction: Infection with H.pylori and gastric acid secretion are required for ulcer formation in most subjects with duodenal ulcer (DU) disease. The level of gastric acid secretion may affect bacterial survival and H. pylori may inhibit gastric acid secretion. Aim: To test whether an equilibrium is reached between the level of antral H.pylori colonisation density and acid secretory capacity in duodenal ulcer and non-ulcer subjects.

Methods: 10 HP+ve patients with no history of DU (10 men, mean age 44 years, range 33-60), 10 HP+ve patients with inactive DU (9 men, mean age 59 years, range 36-71) were studied and the results of 13 HP-ve patients with active DU (11 men, mean age 44 years, range 23-67) were reviewed. At gastroscopy biopsies were taken from the antrum 2 cm proximal to the pylorus and embedded in epoxy resin. Thick sections were stained, viewed with light microscopy and the number of organisms along the epithelial surface were counted using a graticule. Studies of acid output were performed in response to maximal pentagastrin stimulation (6 μg/kg im) and peak acid output (PAO) was calculated.

Results: A negative association was found between bacterial load and PAO in the group with active DU (r = -0.7448, p < 0.01). A negative trend was seen between bacterial load and PAO in the H pylori positive gastritis group (r = 0.537, p < 0.1). No association was found between bacterial load and PAO in the inactive DU group (r = 0.1869, p > 0.2) and no differences in H pylori bacterial load was found between the three groups. Conclusions: In the group of patients with active DU disease bacterial load decreases as acid secretory capacity increases and an equilibrium is reached. This equilibrium is not evident in the group of patients with inactive DU disease. In the H pylori positive gastritis group a trend of negative association is seen between bacterial load and PAO suggesting that an equilibrium is also reached in this group of patients. These findings are consistent with the hypothesis that in DU patients an equilibrium manifests when active ulceration occurs.

THICKNESS OF THE ADHERENT GASTRIC MUCUS GEL LAYER IN MAN IS NOT IMPAIRED BY HELICOBACTER PYLORI INFECTION. J. Newton1,2, N. Jordan1, G. Williams3, J. Pearson1, O James1, A. Allen2, Departments of 1) Physiological Sciences, 2) Medicine University of Newcastle upon Tyne, NE2 4HH.

The continuous adherent mucus gel layer has been proposed as a protective barrier in the stomach and is the home of Helicobacter pylori (HP). The mucus gel is subject to shrinkage and dehydration during conventional histological fixation and so measurement of its thickness is unreliable. It has been proposed that HP infection decreases the thickness of the mucus gel layer predisposing the underlying mucosa to attack from endogenous and exogenous aggressors. Aim: to measure the thickness of the mucus gel layer in sections of human gastric biopsies acquired at endoscopy from subjects with and without HP infection. Methods: cryostat sections were processed with a new histological method which preserves the mucus gel by avoiding the prolonged use of organic solvents and resins. Subjects all had a macroscopically normal stomach at endoscopy, and were not taking acid suppressive drugs or NSAID therapy. 14 HP-ve (mean age 57.3 (SD18.5)), 13 HP+ve (mean age 61 (SD13.5)) were included. All antral biopsies from each subject were processed. Cryostat sections were mounted and stained with PAS/AB. 60 measurements of mucous thickness were made from each subject. Results: A continuous, thick, PAS staining mucus layer was observed at the mucosal surface of all biopsy samples. There was no significant difference in the thickness of the mucus gel layer between HP-ve individuals mean 98.2 μm(SEM11.7) compared to HP+ve individuals 112.3 μm(SEM11.4).

Conclusions: HP infection does not result in a thinner protective mucus barrier. The thickness values obtained in this study compare to those found previously using unfixed mucosal sections. However, our results do not support the conclusion that HP infection impairs the efficacy of the mucus gel barrier.

THE INFLUENCE OF DIET ON MUCOSAL BLOOD FLOW

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The ubiquitous role of nitric oxide (NO) is now widely acknowledged, especially in its effects on vascular tone. We have previously described the phenomenon of chemical generation of NO in the stomach by recirculation of ingested nitrate via the plasma into saliva. Upon secretion a proportion of salivary nitrate is oxidised to nitrite which, when swallowed, to the acidic environment of the stomach generates NO. In contrast to the picotestyle amounts of enzymatically generated NO at cellular level, high (micromolar) quantities are produced by this mechanism.

The aim of this study was to determine whether orally administered nitrate modified gastric mucosal blood flow measured by endoscopic laser doppler blood flowmetry.

Nineteen informed, consenting patients requiring endoscopy for symptoms primarily of gastrointestinal reflux or possible coeliac disease were selected. They were randomised to receive either 2 mmoles of potassium nitrate (test) or potassium chloride (control). Prior to administration of the salt a blood sample was taken. One hour after ingestion a further blood sample was taken, endoscopy performed, initially without air insufflation, and a sample of gastric headspace gas aspirated for measurement of NO. Gastric juice was taken for nitrate and nitrite assay. Four mucosal blood flow measurements were made in each of antrum, body and fundus.

One hour after test salt administration, despite significantly augmented plasma nitrate (mean±SEM test 140±9 micromolar c.f. control 40±4), gastric nitrite (1816±540 c.f. 258±38) and gastric NO (65±10 parts per million c.f. 17±6), all p<0.0001, mucosal blood flow remained steadfastly uniform in all areas. The mean flow in each area in the control and test groups were almost identical (- antrum: - flux units test mean ±SEM = 60±/c.f. control 64±/; body: ±SEM =76±/c.f. 76±/; fundus: ±SEM =115±/c.f.111±/). The lack of vascular response to high NO concentrations was unexpected. A possible explanation is that these high concentrations of NO exceed the regulatory threshold and that under normal circumstances gastric mucosal blood vessels are maximally stimulated by NO. This may imply that NO is not the primary blood flow regulator in this particular vascular bed. Thus this fundamental aspect of gastric physiology is resistant to external influences such as diet.

USE OF THE ROCKALL SCORE TO ASSESS THE EFFECTIVENESS OF AN UPPER GASTROINTESTINAL BLEEDING UNIT.

SGW Jones, R Davies, I Epworth, AG Johnson*, DC Gleeson, AJ Lobo. Gastroenterology and Liver Unit, and *University Department of Surgery, Royal Hallamshire Hospital, Glossop Road, Sheffield, S10 2JF.

The National Audit of acute upper gastrointestinal haemorrhage resulted in the development of a scoring system based on risk factors for dying. This allows the case-mix of patients from different centres to be compared. This “Rockall” risk assessment score was applied to all patients admitted to a specialised upper GI bleeding unit.

Patients and methods: Consecutive patients admitted to an upper GI bleeding unit over 7 months were prospectively analysed. Patients were given an initial score (0-7, Low risk score 0-2, medium risk 3-5, high risk 6-7). Patients who underwent gastroscopy were also given a completion score.

Results: 279 consecutive patients were admitted to the unit of which 212 patients (83.2%) were considered to have had an upper GI haemorrhage. Gastroscopy was performed in 212 patients (91%). The distribution of initial “Rockall” scores did not significantly differ from that in the National Audit (p=0.08). However, patients admitted to the specialised unit had significantly higher complete scores than in the National Audit (Median 5 vs 4, p=0.01). 36 patients (15.5%) had bled from oesophageal varices. 14 patients (6.0%) died compared with the National Audit mortality of 14%. All had significant associated morbidity. Mortality in patients with low, medium and high initial “Rockall” scores was 1%, 9% and 17% respectively in the specialised unit, compared with 3%, 21% and 49% in the National Audit.

Conclusion: A specialised unit is associated with a low mortality from upper gastrointestinal haemorrhage. This is despite a greater proportion of high-risk patients than the National Audit.

UPPER GI HEMORRHAGE CAN BE SAFELY MANAGED USING A DEFINED, RISK BASED PROTOCOL


Purpose: A six month audit was undertaken to assess the success of a management protocol for upper GI haemorrhage in our hospital.

Methods: According to the protocol, patients are categorised according to risk status into shocked (pulse > 100 bpm or systolic bp < 100 mmHg), high risk (age > 60, Hb < 10 g/dl or coexistent cardiovascular disease), or low risk (all others). Depending on status, patients are admitted to either a surgical, specialised GI, or general medical ward, with early endoscopy and intensive monitoring. More conservative management is used in low risk cases. Details of all upper GI bleeds (including those occurring in in-patients) occurring between April 1995 and September 1995 were collected prospectively from casualty records, endoscopy records and discharge diagnostic coding. Notes were reviewed retrospectively.

Results: 89.9% of all case records requested were reviewed (253 cases of upper GI haemorrhage). Mean age was 59.0 years, with 19.3% of cases over 80 years. Endoscopy was performed in 81.6% of all cases, 91.2% of shocked patients, 86.3% of high risk, and 68.4% of low risk patients. 85.2% of endoscopies were within 24 hours of the bleed. Rebleed rate was 5.9%, operative rate was 2.4% and mortality rate was 10.5% (3.4% for new patients; 40.0% for existing in-patients).

Results according to risk are tabulated below:

<table>
<thead>
<tr>
<th>Risk Status</th>
<th>Patients (%)</th>
<th>Rebleed rate (%)</th>
<th>Operative rate (%)</th>
<th>Mortality rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>79 (31.2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>High risk</td>
<td>117 (46.2)</td>
<td>8 (6.8)</td>
<td>0 (0)</td>
<td>16 (13.7)</td>
</tr>
<tr>
<td>Shocked</td>
<td>57 (22.5)</td>
<td>7 (12.3)</td>
<td>5 (8.8)</td>
<td>9 (15.8)</td>
</tr>
</tbody>
</table>

Conclusions: Favourable results can be achieved in upper GI haemorrhage by intensifying management according to a risk based protocol, without the use of a specialised bleeding unit. Patients with low risk status can safely be managed more conservatively.

EFFECTIVE USE OF THROMBIN IN ARRESTING GASTRIC VARICEAL HEMORRHAGE.

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Background: Thrombin has been proposed as an effective second-line agent in the management of bleeding gastric varices, but in the only published series of its use most were not actively bleeding at the time of endoscopy. We report our experience using thrombin in 10 patients, all with actively bleeding gastric varices at initial endoscopy.

Patients and Methods: Ten patients (7 male, 3 female, mean age of 48.5 yr; range: 34 to 71 yr) with bleeding gastric varices were treated by intravascular injection of bovine thrombin (100 U/ml, Armour Pharmaceuticals) using a standard injection cannula (Microvarice). Six had a diagnosis of alcohol-induced cirrhosis, three viral hepatitis and one secondary biliary cirrhosis. Five patients were Child’s Grade C, 2 grade B and 3 grade A. seven patients had previously undergone sclerotherapy or banding of oesophageal varices.

Results: A bleeding gastric varix was identified at the fundus in six patients and lesser curve in four. Bovine thrombin was injected at 1 to 5 sites (median 3.0) using a mean total volume of 8.6 ml (range: 4 to 20 ml). Initial haemostasis was achieved in all cases. Nine of the patients had also large (grade II-IV) oesophageal varices which were treated by either banding ligation or ethanolamine injection and eight patients received an octreotide infusion for 24 hr. Early rebleeding occurred in four patients: three from gastric varices which were successfully re-injected with thrombin and one from portal hypertensive gastropathy. After a median follow-up of five months (range 2 to 7.5 months) no patients have had further bleeding from a gastric varix. Four of the patients with Child’s Grade C cirrhosis died from causes other than bleeding (sepsis in three and hepatorenal syndrome in one).

Conclusions: Thrombin appears to be a highly effective means of achieving haemostasis in patients with bleeding gastric varices and should be available for use where banding or tissue adhesives have failed or are not available.

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A prospective, randomized and stratified study was performed in 13 centers in 9 European countries. Patients fulfilling the inclusion criteria ulcer hemorrhage with spurting, oozing or a non-bleeding visible vessel were randomly allocated after pretreatment with epinephrine to receive single injection therapy with fibrin glue (FG), repeated therapy with FG or single sclerotherapy with Polidocanol 1% as a control group. A daily repeat endoscopic control was performed until the ulcer base presented hematin covered or clean (Forest IIC or III).

A per protocol analysis was performed on 737 patients with a minimum observation period of 5 days and a safety follow-up of one month. Primary efficacy criterion was rebleeding after initial hemostasis defined as bleeding from the same source, visually verified at endoscopy or laparotomy. The rebleeding rate for FG repeated injection was 12.1%, FG single injection 17.2% and for Polidocanol 21.3%, statistically different from the FG repeat group (p<0.01, two-sided). Half of the rebleeds occurred within 24 hours after initial hemostasis, before the scheduled repeat endoscopy. Safety analysis as well as evaluation of laboratory parameters and clinical variables revealed no specific risk for either treatment group.

Conclusion: Repeat injections of FG significantly reduce rebleeding. Early repeat endoscopy with profylactic re-treatment might be beneficial.

REDUCTION IN SERUM OESTROGENS WITH FASTER INTESTINAL TRANSIT. SJ Lewis, RE Oakley, HHG McGarrigle, KW Heaton. 1Dept of Medicine, Bristol Royal Infirmary. 2SAS Centre for Steroid Hormones, Leeds General Infirmary. 3Dept of Obs & Gynae, University College London.

Any factor limiting reabsorption of oestrogens from the colon should lead to increased faecal excretion of oestrogen and reduced levels of serum oestrogens. High fibre diets and wheat bran supplements reduce serum oestrogens, perhaps explaining reported associations between high fibre intake and reduced risk of breast cancer. We hypothesised that dietary fibre reduces serum oestrogen concentrations by speeding colonic transit, reducing the time for bacterial deconjugation (by β-glucuronidase a pH dependent enzyme) and/or reabsorption of oestrogens. To test this we altered whole gut transit times (WGT) in 5 ways and looked for changes in serum oestrogen and in stool pH and β-glucuronidase activity.

40 healthy premenopausal volunteers were randomised to one of 3 groups. Ten subjects took senna, then after a washout period wheat bran, both for 2 menstrual cycles. Another 10 did the reverse. A third group of 20 subjects took loperamide to slow down transit for two cycles. All supplements were taken in the maximum tolerated dose. At the beginning and end of each study period blood was taken for oestrogens (day 6 of the menstrual cycle), a 4 day dietary record was kept, WGT was measured and stools were analysed for pH and β-glucuronidase activity.

Serum oestriol sulphate, the major storage form of oestrogen, fell with wheat bran (average dose 20g/day) and with senna; both unconjugated and non-protein bound oestriol fell only with senna. No significant changes in serum oestrogens occurred with loperamide. Senna and loperamide caused significant alterations in WGT; changes in those taking wheat bran supplemented tended towards a reduction (p<0.05). No significant changes were seen in faecal β-glucuronidase activity. Stool pH changed only with senna, where it fell. There was no significant change in dietary intake.

<table>
<thead>
<tr>
<th>Changes in geometric means of serum oestrogens (pg/ml)</th>
<th>p&lt;0.05</th>
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</thead>
<tbody>
<tr>
<td>Oestradiol</td>
<td>Oestrone</td>
</tr>
<tr>
<td>3rd End</td>
<td>1st Start</td>
</tr>
<tr>
<td>Wheat bran</td>
<td></td>
</tr>
<tr>
<td>281</td>
<td>262</td>
</tr>
<tr>
<td>Senna</td>
<td></td>
</tr>
<tr>
<td>261</td>
<td>226</td>
</tr>
<tr>
<td>Loperamide</td>
<td></td>
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<tr>
<td>233</td>
<td>249</td>
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Speeding up intestinal transit can lower serum oestrogens. Faster intestinal transit may explain the epidemiological association of low risk of breast cancer with a high fibre intake.