Pharmacology and therapeutics W33–W39

W33

HELICOBACTER (H) PYLORI AND PEPTIC ULCERS IN RHEUMATOID ARTHRITIS PATIENTS RECEIVING NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAID) AND GOLD OR SULPHASALAZINE.

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The conflicting reports on Gold and H pylori could be related to the use of serological tests of unproven value in NSAID patients, and to the lack of the appropriate control groups. More importantly, the endoscopic consequences of the possible effect of Gold on H pylori have not been investigated. We studied the prevalence of H pylori and peptic ulcers in patients with rheumatoid arthritis being treated with NSAID only and NSAID plus intramuscular Gold. Another control group was included, which consisted of patients receiving NSAID plus Sulphasalazine. Both Gold and Sulphasalazine are known to have similar anti-inflammatory activity. NSAID, Gold and Sulphasalazine had to be taken for at least six months. At endoscopy, gastric antral biopsies were taken to check for H pylori by both histology and bacteriology. The endoscopic abnormalities were divided into ulcers (three dimensional lesions measuring at least 5 mm) and erosions (small bidimensional lesions). All assessments were carried out under randomised conditions.

RESULTS; the characteristics and findings of 85 patients were as follows:

	NSAID only(I)	Sulphasalazine+NSAID(II)	Gold+NSAID(III)
Number	31	27	27
Median(years)	55	51	60
Smokers	11	12	8
Ulcers	12	9	3*
Erosions	6	5	8
H.pylori	17	21	9*

* p<0.05, analysis of variance, versus I and II

Conclusions; Patients treated with Gold and NSAID had the lowest prevalence of H pylori. This could explain the apparent reduction in the prevalence of peptic ulcers in this group, and might have therapeutic implications.

W34

URINE ENZYME PROFILES AS INDICATORS OF RENAL TUBULAR DYSFUNCTION IN INFLAMMATORY BOWEL DISEASE (ID).

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Renal toxicity is a potentially serious new side effect of pH dependent release systems of 5-ASA. Most reports describe interstitial nephritis with renal failure in which case it may be possible to detect subclinical damage with sensitive tubular tests. We studied gamma glutamyl transferase (GGT), alkaline phosphatase (AP) and alanine amino peptidase (AAP) (brush border), Lactate dehydrogenase (LDH) (cytosolic) and N-acetyl glucosaminidase (NAG) (lysosomal) enzyme activities in urine from 40 controls, 32 patients with IBD not on 5-ASA compounds and 36 patients on mesalazine (Asacol). All had normal S-urea and creatinine. Urines were cleaned up within 1 hour of voiding. The normal upper limits (M+/-SD) of GGT, AP, AAP, LDH and NAG were 4.02, 1.46, 1.44, 1.97 and 38.9 U/mmol creatinine, respectively. Of the patients untreated with 5-ASA 10 (31%)had a single and 1 (3%) two enzymes elevated but NAG was normal in all. Seven (19%)patients on mesalazine had one, 6 (17%) had two and 7 (17%) had 3 or 4 enzymes elevated. Six patients had elevated NAG. The more enzymes that were abnormal in an individual the higher the activity. These studies demonstrate frequent isolated abnormalities of urinary enzymes in patients with IBD not on 5-ASA which may indicate preexisting tubular disease. Patients on mesalazine had significantly more enzymes elevated and to a greater extent, raising the possibility that mesalazine may be causing or exacerbating subclinical renal damage.

W35

Long term (>6 months) acid suppressing therapy in patients in general practice. Reasons for treatment and investigation: the scope of the problem.

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Powerful acid suppressing therapy has revolutionised the treatment of peptic ulcer disease. The drugs used are expensive and there is disagreement about their correct role in the long term management of acid related disorders.

22 419 patients in 3 general practices in the Harrow area were studied. All patients having continuous treatment with H2 antagonists or omeprazole were identified from repeat prescribing data and records were studied to determine investigations and indications for therapy.

239 (1.06%) were taking long term treatment. Positive diagnosis of peptic disease had been obtained in 133 (56%), DU 79, GU 12, oesophagitis 28 and oesophageal stricture 14. 22 (9.2%) were treated as prophylaxis (11 NSAID, 7 steroids and 4 for serious medical conditions). 3 patients had oesophageal motility disorders. 19 (8%) had endoscopic /histological diagnoses of gastritis (12) or duodenitis (7). 15 (6%) patients had a diagnosis of hiatus hernia and 47 (19.6%) had abdominal pain (25 with negative investigations and 22 no investigations).

81% of patients were taking ranitidine, 14% cimetidine and 5% other treatment.

The second commonest cause for long term H2 antagonist prescribing was non-ulcer dyspepsia/undiagnosed abdominal pain. This finding has considerable clinical and financial implications. Guide-lines for investigation and treatment of dyspepsia need to be agreed and implemented locally in order that appropriate prescribing of these drugs can be achieved.

W36

THE EFFECT OF MISOPROSTOL ON ENTEROSCOPY-DIAGNOSED NSAID SMALL BOWEL ENTEROPATHY - A RETROSPECTIVE STUDY.

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50 patients on long-term NSAID therapy with iron deficiency anaemia had sonde-type enteroscopy. 26 were found to have NSAID enteropathy (small bowel ulcers, erosions, red spot lesions). After enteroscopy, 24 of these patients continued to attend the Rheumatology clinic - 2 patients were lost to follow-up. We have retrospectively studied the use of misoprostol and the change in haemoglobin of these patients.

3 of the 24 patients discontinued NSAIDs following the discovery of enteropathy. Of the remaining 21, who continued on NSAID therapy, 11 were treated with misoprostol (400-800 µg/day) and 10 were not given misoprostol. These two groups were comparable for severity of enteropathy, iron supplementation and change of 'second-line' drug therapy.

In the 11 misoprostol-treated patients, the haemoglobin rose significantly from median 9.1 (range 6.2 - 10.6)g/dl to median 10.6 (range 6.5 - 16.8)g/dl (p = 0.008)*. In the patients receiving no misoprostol, the haemoglobin fell but not significantly, from median 9.1 (range 7.5 - 10.6)g/dl to median 8.1 (range 5.6 - 14.7)g/dl (p = N.S.)*.

The difference between these two groups suggests that small bowel blood loss due to NSAIDs is reduced by misoprostol therapy, even when NSAIDs are continued. These findings lend support to the proposition that misoprostol may promote the healing of NSAID enteropathy.

*Wilcoxon matched pair signed rank test.

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W37

LACK OF EFFECT OF HIGH DOSE RANITIDINE ON THE POST-PRANDIAL PHARMACOKINETICS OF ALCOHOL

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Several studies have suggested that H_2-receptor antagonists may affect the rate or extent of absorption of alcohol. Various factors, such as time of day, gender, presence of food etc, may affect the absorption or metabolism of alcohol and hence may influence the results of interaction studies. The present double-blind two-way crossover study compared the effects of ranitidine 300mg qds and placebo on a single post-prandial dose of alcohol ($0.5g.kg^{-1}$) given at 3 different times of day to 18 normal caucasian male subjects (aged 25-45 years).

Medication started on day 1 and continued up to and including day 8. On day 4 a standard breakfast at 0745h preceded the 0800h dose of medication and the alcohol ($1.6mL.kg^{-1}$ vodka, 40%, made up to 200mL with orange juice) at 0830h. Eleven blood samples were taken at frequent intervals up to 1230h. These were rapidly frozen to await analysis by a fully validated GLC assay. Psychomotor tests, including digit symbol substitution and assessment of alertness using rating scales were carried out 10 min prior to alcohol and at 30, 60, 120 and 240 min after alcohol consumption. On day 6 a standard lunch was eaten at 1245h followed by the above procedures and similarly on day 8 after a standard dinner at 1745h.

There were no statistically significant differences between the effects of ranitidine and placebo on the psychomotor test results (MANOVA) or on alcohol C_{max}, AUC or t_{max} at breakfast, lunch or dinner time (ANOVA). Mean (±SD) results for C_{max} and AUC were:-

Parameter	Medication	Breakfast	Lunch	Dinner
AUC ($mg.h.L^{-1}$)	ranitidine	1123 (370)	1128 (380)	1007 (384)
	placebo	1115 (349)	1096 (458)	949 (384)
C_{max} ($mg.L^{-1}$)	ranitidine	464 (162)	487 (166)	438 (145)
	placebo	437 (102)	454 (164)	413 (151)

In conclusion, high dose ranitidine has no significant effect on blood alcohol concentrations or psychomotor function after a single dose of alcohol ($0.5g.kg^{-1}$) taken at breakfast, lunch or dinner time.

W39

QUANTIFICATION OF GASTROINTESTINAL BLOOD LOSS FOLLOWING THROMBOLYTIC THERAPY FOR ACUTE MYOCARDIAL INFARCTION

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Thrombolytic therapy has revolutionised the management of acute myocardial infarction, but is not free from adverse effects, the most common being bleeding. Gastro-intestinal blood loss is a well known complication, but usually recognised only when severe. Trace (subclinical) amounts of blood are lost from the gut in health. We wished to determine whether thrombolytic therapy with streptokinase or tissue plasminogen activator enhanced subclinical blood loss from the gut.

Serial daily stool samples were collected for up to 5 days from 57 patients admitted to the cardiac care unit with suspected myocardial infarction. Patients with a previously known gastrointestinal disorder likely to predispose to bleeding, as well as those with such bleeding at admission were excluded from the study. Stool haemoglobin concentrations were determined by measuring haeme derived porphyrins using fluorescence spectrometry. Each sample was measured three times and the mean calculated and expressed as mg of haemoglobin per gm of stool (mg/g).

A total of 88 stool samples were collected from 57 patients (42 male) aged between 34 and 85 years. Thirty eight patients received either streptokinase or tissue plasminogen activator, while 19 did not. However, some of the latter group did receive aspirin, warfarin or heparin. The faecal haemoglobin concentration in the group receiving thrombolytic therapy was 3.65 (2.2 - 5.1) mg/g (mean (95% confidence intervals)), while in the group not given thrombolytic therapy it was 1.45 (0.8 - 2.10). These differences were significant P=0.01 (Mann-Whitney U test).

These results suggest that thrombolytic therapy for acute myocardial infarction is associated with a significant increase in sub clinical blood loss from the gut.

Small bowel/nutrition W40–W51

W38

BONE MARROW TOXICITY FROM AZATHIOPRINE IN INFLAMMATORY BOWEL DISEASE: EXPERIENCE FROM 1663 PATIENT YEARS OF THERAPY.

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Although azathioprine has been shown to be helpful in the treatment of ulcerative colitis and Crohn's disease, bone marrow suppression may result in serious sequelae. We report here the experience of bone marrow toxicity in 739 patients treated at one hospital for inflammatory bowel disease with azathioprine over 27 years.

Methods: Between 1964 and 1991, 416 patients with Crohn's disease, 298 with ulcerative colitis and 34 with indeterminate colitis were treated with azathioprine (dose 2 mg/kg). Their case histories and corresponding blood counts which were performed regularly were reviewed.

Results: Leucopenia (WBC < 3.0) occurred in 28 patients (3.8%) necessitating azathioprine cessation or dose reduction. All 19 patients whose WBC remained above 2.0 were asymptomatic. Of the other 9 subjects (1.2%) in whom leucopenia was more severe (WBC < 2.0), 4 remained asymptomatic and 5 developed complications related to marrow aplasia (2 of these cases died). Severe leucopenia occurred at any time during azathioprine therapy (0.5-132 months after its introduction; mean=27.1 months), developing abruptly in 6 of the 9 cases and gradually in all other 3. Thrombocytopaenia (platelet count < 100,000) resulted in the withdrawal of azathioprine in 17 cases, 8 of whom had accompanying leucopenia. Only one individual developed symptoms related to thrombocytopaenia.

Conclusions & Recommendations: There is a definite but small risk of bone marrow complications with azathioprine for inflammatory bowel patients. Leucopenia is more common and significant than thrombocytopaenia. Bone marrow suppression may develop abruptly or gradually and can occur at any time during azathioprine treatment. Monitoring of the full blood count should be performed monthly throughout azathioprine therapy. In this way, asymptomatic patients with bone marrow suppression can be detected before serious complications develop. Dosage modifications are required when the WBC falls below 3.0 or platelet counts are less than 100,000.

W40

ANTIGLIADIN ANTIBODIES IN BLOOD DONORS IN NORTHERN IRELAND

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The prevalence of coeliac disease reported in the literature ranges from 1:300 to 1:2000 but these figures are based on detected symptomatic cases. Using an ELISA method for detection of antigliadin IgA, which has high sensitivity and specificity for coeliac disease (BMJ 1991; 303: 1163-5), we studied sera from 443 blood donors attending 11 centres in Northern Ireland. Patient ages ranged from 17 to 64 with a mean (SD) of 36 (11); 295 (67%) were male.

Five donors (1%) had positive values (≥ 100 ELISA units) ranging from 132 to 300. There appeared to be clustering of positive values among donors attending centres in the north-west (4 of 191 donors v. 1 of 252 elsewhere), although mean (SD) values were not significantly higher (27 (36) in the north-west v. 21 (25) elsewhere).

Thus, even amongst a blood donor population in Northern Ireland, from which anaemic patients are excluded, the prevalence of coeliac disease estimated from a highly sensitive and specific serum antigliadin IgA assay is 1:100 and may be higher in some areas. Testing patients with vague or atypical symptoms therefore seems worthwhile. However, the risks of long-term complications and the benefits of dietary gluten exclusion in asymptomatic patients are unknown and the need for serological screening, jejunal biopsy and treatment in this group is unclear.

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