LACK OF EFFECT OF HIGH DOSE RANITIDINE ON THE POST-PRANDIAL PHARMACOKINETICS OF ALCOHOL
S Toon, A Khan, S Langley, F Mulkins, M Rowland (introduced by I Turnberg)
Medeval and the Department of Pharmacy, both University of Manchester

Several studies have suggested that H2-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 25-65). Medication started on day 1 and continued up to and including day 8. On day 4 a standard breakfast at 0745 preceded the 0800h dose of medication and the alcohol (1.6LmL-1) vodka, 40%, made up to 200mL with orange juice) at 0830h. 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. After this 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 Cmax, AUC and alcohol concentrations (ANOVA). Mean (SD) results for Cmax and AUC were:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Medication</th>
<th>Breakfast</th>
<th>Lunch</th>
<th>Dinner</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>ranitidine</td>
<td>1123 (370)</td>
<td>1182 (380)</td>
<td>1007 (384)</td>
</tr>
<tr>
<td>(mg.L-1)</td>
<td>placebo</td>
<td>1115 (349)</td>
<td>1096 (458)</td>
<td>949 (384)</td>
</tr>
<tr>
<td>Cmax</td>
<td>ranitidine</td>
<td>464 (162)</td>
<td>487 (166)</td>
<td>438 (145)</td>
</tr>
<tr>
<td>(mg.L-1)</td>
<td>placebo</td>
<td>437 (102)</td>
<td>454 (164)</td>
<td>413 (151)</td>
</tr>
</tbody>
</table>

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.

Small bowel/nutrition W40-W51

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. Thrombocytopenia (platelet count<100,000) resulted in the withdrawal of azathioprine in 17 cases, 8 of whom had accompanied bone marrow suppression. One individual had received bone marrow suppression from a single episode of thrombocytopenia. Conclusions & Recommendations: There is a definite but small risk of bone marrow suppression associated with azathioprine in inflammatory bowel patients. Leucopenia is more common and significant than thrombocytopenia. 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.

QUANTIFICATION OF GASTROINTESTINAL BLOOD LOSS FOLLOWING THROMBOLYTIC THERAPY FOR ACUTE MYOCARDIAL INFARCTION
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Royal Devon & Exeter Hospital, Exeter

Thrombolytic therapy has revolutionized the management of acute myocardial infarction, but is not free from adverse effects, the most common being bleeding. Gastrointestinal blood loss is a well known complication, but usually recognized 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 58 stool samples were collected from 57 patients (2 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 interval)), while in the group not given thrombolytic therapy it was 1.42 (0.8 - 2.1). 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 subclinical blood loss from the gut.

Small bowel/nutrition W40
The relationship of cell volume to cell height and width: a comparative study by computerized image analysis.


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In various malabsorption syndromes in which mucosal flattening occurs, the surface enterocytes are reduced in height (height profile). However, because of altered epithelial cell proliferation-dynamics, in which cell losses from the flattened surface may exceed production, the apparent reduction in cell height may merely reflect increased coverage of basement membrane, resulting in a more squamous-type cell, but without necessarily altering its volume. These possibilities have been explored with the use of computerized image analysis of appropriate small intestinal biopsy specimens. Methods: 1 μm toluidine-blue-stained epon sections of upper jejunal mucosa from 21 disease-controls (Group I) and 20 untreated coeliac patients (Group II) were analysed in terms of enterocyte height; width; area and volume. For the latter, cells were either assumed to be cylinders (I), or inverted truncated cones (II). Similar dimensions for enterocyte nuclei were calculated based on an assumed shape of prolate spheroids. Results: There were significant differences in cell height (37 vs 33μm: p<0.001), cell width (5.1 vs 4.7μm: p<0.001), cell area (184 vs 152μm²: p<0.0001) and cell volume (790 vs 604μm³: p=0.0001) but not cell thickness. Conclusions: 1. Cell volume of untreated coeliac mucosa is reduced in comparison with normal mucosa. 2. Average cell width correlates best with cell volume, rather than height. 3. Random measurement of epithelial "barrier" width is equally effective as the measurement of the mean heights of individual cells.
Thus, inactive compared with controls between groups. Of patients kg/in², Weight, BMI circumference ceased growing measurements previous 12 (age subject 15.3±2.8%, p<0.05). Six CDC to disease that may reflect functional changes.

GROWTH IN CROHNS’ DISEASE (CD) IS ASSOCIATED WITH HIGHER ENERGY REQUIREMENTS. G Zoli, PH Katerias, JS Garrow, MIG Farthing, St Bartholomew’s & St Mark’s Hospitals, London, UK.

Growth failure occurs in up to 30% of adolescents with CD. Deficiency of dietary energy substrates appears to be a major contributor, but the energy requirements of these patients is unclear. Six adolescents with inactive CD, assessed to being greater during the previous 12 months (group A, mean age 17.3 yrs), five who had ceased growing (group B, mean age 19.6) and 6 growing healthy controls (age and sex matched with group A) were studied. In each subjects nutritional status was assessed by anthropometric measurements from which body mass index (BMI), arm muscle circumference (AMC), fat percentage and fat free mass (FFM) were calculated. Resting energy expenditure (REE) was measured with subjects fasted using a Deltrac indirect calorimeter. Weight, BMI and fat percentage were significantly reduced in patients of both group A (mean 51.5±4.8 kg, 19.3±1 kg/m², 13.6±2.8%, p<0.05) and group B (56.4±2.5 kg, 20.1±1 kg/m², 15.3±2.8%, p<0.05) compared with controls (63.4±3.4 kg, 23.5±0.5 kg/m², 22.5±2.3%). FFM and AMC were not different between groups. REE/kg of body weight was significantly higher in group A (31.7±2.3 kcal/kg/24h, p<0.001) but not group B (26.5±1.1 kcal/kg/24h, p=0.13). No difference was found between the two groups of patients. However, REE/kg FFM was significantly higher in patients in group A (36.3±2.1 kcal/kg/24h, p<0.05) compared with patients in group B (31.5±0.7) and controls (31.0±1).

These results suggest that (i) lower body weights in adolescents with inactive CD is due to a reduction of fat mass and (ii) such subjects who are growing significantly higher energy expenditure. Thus, although food intake may appear adequate, it is appropriate to consider nutritional supplementation in adolescents with CD.

A PREMEAL OF L-PHENYLALANINE RELEASES CHOLECYSTOKININ AND REDUCES SUBSEQUENT FOOD INTAKE IN HUMANS. AB Ballinger, ML Clark, Dept. Gastroenterology, St Bartholomew’s Hospital, London UK.

Exogenous administration of cholecystokinin (CCK) reduces food intake in humans. Oral administration of L-phenylalanine increases endogenous secretion of CCK from the duodenum. The aim of this study was to investigate the effect of oral L-phenylalanine on food intake in humans. Methods: On separate occasions 6 non-obese fasted subjects were given a pre-load of 10g L-phenylalanine or placebo 20 min before being presented with a standard test meal of known calorie content. The amount of food offered was far in excess of the amount subjects were likely to eat. Preliminary experiments had shown that peak plasma concentrations of CCK were obtained 20 min after giving L-phenylalanine. The test meal was given to coincide with this peak. Visual analogue scales to assess hunger, fullness and desire to eat were completed pre-meal, post-meal and at hourly intervals thereafter for 5h. Blood was taken before giving phenylalanine/placebo, immediately pre- and post-meal and stored for CCK by bioassay. The total number of calories consumed was determined. Results: Total calorie intake (mean ± SEM) after placebo was 1587±174 kcal compared to 1089±122 kcal after a phenylalanine pre-load (p<0.03). Visual analogue scales to assess hunger and desire to eat did not predict subsequent food intake. Basal levels of CCK were 1.10 ± 0.12 pmol/l; 20 min after the phenylalanine pre-load CCK levels increased to 5.49 ± 0.83 pmol/l. There was no increase in CCK following placebo (0.99 ± 0.06 pmol/l; p<0.04). Conclusions: Pre-prandial administration of L-phenylalanine resulted in a rise in plasma concentration of CCK and this was associated with a significant reduction in food intake. These results suggest that the effect was due to the early rise of CCK induced by phenylalanine and that endogenous CCK is a major regulator of food intake in humans.

INSULIN IMPROVES NITROGEN BALANCE OVER AND ABOVE OPTIMAL PARENTERAL NUTRITION. Ann RNW, Halliday Dr, Walsall, Powdl-Tuck L. Departments of Human Nutrition and Sports Medicine*, Royal London Hospital, Whitechapel, London E1.2AD. Nutrition Research Group*, Clinical Research Centre, Watford Road, Harrow HA1 JUX.

Nutrition must be given parenterally in conditions associated with obstruction or malabsorption in the gut. Despite the provision of adequate calories and nitrogen negative nitrogen balance will persist if there is superimposing infection or cancer. Insulin has been shown to be anabolic in animals in vivo and in humans in vitro. We wish to observe any additional effect of insulin on nitrogen balance in the parenterally fed state. 5 healthy male volunteers were fed parenterally for about 20 hours with a balanced feed providing approximately 1.3 times Resting Energy Expenditure and 12.4 grams nitrogen per 24 hours. After a mean run in period of 11 (6-15) hours whole body protein turnover was measured over 2 periods of 2 hours using constant 13C-leucine infusion technique. In random order turnover was measured on and off a eucaloric hyperinsulinaemic clamp employing an infusion of 40uE/m2 body surface area/min atractipin insulin and a variable intravenous infusion of potato starch glucose to establish hyperinsulinaemia with stable glucose levels. The mean and standard error of the mean of the rates of leucine flux calculated from plasma 13C-ketoisocaproate (QKIC), oxidation of leucine (Oxid), synthesis of leucine into protein (S) and leucine appearance (A) are expressed as umol/kg/hr.

<table>
<thead>
<tr>
<th></th>
<th>plasma</th>
<th>QKIC</th>
<th>Oxid*</th>
<th>S</th>
<th>S-A*</th>
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<tbody>
<tr>
<td>clamp (m)</td>
<td>84</td>
<td>141</td>
<td>22</td>
<td>119</td>
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<tr>
<td>(s)</td>
<td>12</td>
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<tr>
<td>no clamp (m)</td>
<td>18</td>
<td>151</td>
<td>26</td>
<td>122</td>
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<tr>
<td>(s)</td>
<td>8</td>
<td>7</td>
<td>2</td>
<td>7</td>
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</tbody>
</table>

Infusion of supraphysiological doses of insulin results in decreased oxidation of leucine and increased net nitrogen turnover and above that achieved by parenteral feeding and may thus prove to be a useful adjunct in catabolic states.
British Society of Gastroenterology

W50

TOTAL URINARY NITROGEN MEASUREMENT BY NEAR INFRARED REFLECTOMETRY, COMPARISON WITH CHEMICAL METHODS.

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Chemical methods for the measurement of total nitrogen in urine are complex and therefore rarely used; urea nitrogen is the most used alternative, but it often underestimates urinary losses. Aim of this study was to assess the analytical efficacy of near infrared reflectance (NIRA) in the measurement of total urinary nitrogen. This method provides the results in a few minutes, simply injecting the sample in a termocell of the equipment. The comparison was made with both fresh urines (40 samples: 28 from GI patients, 8 of whom on enteral and 5 on total parenteral nutrition; 4 operated, 4 nephrotic and 4 burned patients) and on thawed urines (70 samples from GI patients, 20 of whom in enteral, 8 in total parenteral nutrition). These had to be acidified and warmed to obtain a clear solution. Two different calibration curves had to be obtained for fresh and thawed urines. This was done by a multiparametric regression, compared the results of the Kjeldahl method with those obtained by NIRA on several values at 10.5% of nitrogen. Results: we found a range of NIRA nitrogen concentration of 0.35-2.04% in fresh, of 0.1-1.7% in thawed urines. A coefficient of determination of 0.99 was obtained between the mineralometric and the NIRA nitrogen concentration in fresh and thawed urines respectively. An intrasay coefficient of variation of 6.8% of variation of 6.8% and of 9.0% was found for fresh and thawed urines respectively (3 samples measured 20 times). In fresh urines, a correlation coefficient of 0.93 was found between the NIRA total nitrogen and the urea nitrogen. In conclusion, the near infrared reflectance analysis represents a quick and reliable alternative to the complex chemical methods for the day-by-day study of the nitrogen balance.

W51

ETHANOL FLUSH FOR THE PREVENTION OF CATHETER OCCLUSION

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95, Scotland, UK.

Catheter occlusion by lipid material has been associated with the use of compounded nutrient solution containing lipid. We have studied 51 patients in whom either a saline or enalapril was used prior to a heparin lock in patients receiving parenteral nutrition with such solutions in order to determine whether improved occlusion was achieved. The incidence of catheter occlusion could be achieved.

METHOD

Following overnight infusion of parenteral nutrition, the giving set was disconnected from the extension set and either 20 ml of isotonic saline solution (10 ml aqueous solution of 20% ethanol (m/e) was flushed through the catheter. A aliquot was then placed on the extension set and a heparin lock of 5,000 units heparin was injected through the spigot. Catheter occlusion was recognised by increasing resistance during the flush or by activation of the occlusion alarm of the infusion pump. Catheters were removed if they were occluded, or if there was no further need for parenteral nutrition.

RESULTS

The incidence of catheter occlusion was significantly (p<0.01, X2 test) lower in patients who received the ethanol flush compared with patients who received the saline flush (13/25). In addition catheter survival was significantly (p<0.1, logrank test) longer in patients who received the ethanol flush. No complications of the flushes were observed in either group.

CONCLUSION

Ethanol flush is a simple, safe and effective method of reducing the incidence of catheter occlusion with compounded solutions.