W29

CAN CISAPRIDE OVERCOME THE EFFECTS OF OCTREOTIDE ON INTESTINAL TRANSIT, THEREBY REDUCING THE PROPORTION OF DEOXYCHOLIC ACID IN BILE AND SERUM, AND THE RISK OF GALLSTONEFORMATION?

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Background. In addition to its effect on gallbladder (GB) emptying, we have shown recently that, octreotide (OT) prolongs intestinal transit, and increases the proportion of deoxycholic acid (%DCA) and the cholesterol saturation of GB bile – factors important in the pathogenesis of OT-induced GB stones (GBS). It seems important, therefore, to see whether the probiotic drug, cisapride, might overcome the adverse effects of OT on intestinal transit, thereby preventing the rise in %DCA.

Methods. Therefore, in 8 acromegalic patients (age 22-69, 4 women) receiving long-term OT (LTOT), we used a randomized, double-blind, placebo-controlled, cross-over design to study the effect of cisapride (10mg qds for 2 weeks) on (i) mouth-to-caecum transit time (MCTT) measured by the breath hydrogen technique; (ii) large bowel transit time (LBTT) measured using marker shapes, and (iii) the %DCA in fasting serum (since there is an exchange, and ultimately an equilibrium, between bile acids in serum and bile). We then compared these results with those obtained in 8 acromegalic (age 30-69, 4 women) untreated with OT.

Results. Mean values ± SEM

<table>
<thead>
<tr>
<th>Acromegalic Patients</th>
<th>no OT</th>
<th>LTOT + placebo</th>
<th>LTOT + cisapride</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCTT (min)</td>
<td>171±14.3 **</td>
<td>268±18.3</td>
<td>133±17.1 **</td>
</tr>
<tr>
<td>LBTT (h)</td>
<td>39±4.9 *</td>
<td>54±4.3</td>
<td>30±4.4 **</td>
</tr>
<tr>
<td>%DCA %</td>
<td>15±1.8</td>
<td>24±2.9</td>
<td>13±4.5 *</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.005 compared to LTOT + placebo. For all 3 groups, there was a significant linear relationship between LTOT and %DCA (r=0.76, p=0.005).

Conclusions. These results clearly show that cisapride reverses the effects of OT on both small and large bowel transit, prevents the rise in %DCA in serum, and by implication, the %DCA in bile. If changes in intestinal transit are rate-limiting in the pathogenesis of OT-induced GBs, cisapride should prevent stone formation.

W30

MOTILITY AND COLORECTAL DISEASES

W31

IS THERE A RELATIONSHIP BETWEEN ANAL MUCOSAL ELECTROSENSITIVITY AND ANAL SPHINCTER DEFECTS IN PATIENTS WITH FAECCAL INCONTINENCE (FD)?

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The aetiopathogenesis of faecal incontinence has yet to be fully elucidated. Two important factors in the maintenance of continence are the structural integrity of the internal (IAS) and external (EAS) anal sphincters and anal canal sensation. In patients with FI due to sphincter defects, it is not known whether anal canal sensation is altered and may contribute to the physiological dysfunction. The aim of this study was to study the relationship between MES and sphincter defects in patients with FI. 138 Patients (15M, 143F; median age 56y [IQR: 34-69]) with grade III/IV were studied. All patients underwent endoanal ultrasound (EAS) using a 7.5 MHZ rotating probe and MES testing.

The latter was performed by passing a direct current through a mucosal electrode placed in contact with anal mucosa and measuring the resulting electromyographic activity. Sensitivity was measured in the upper, middle and lower anal canal. There was a sphincter defect in 95 patients (IAS: 10, EAS: 41; both: 44). MES was impaired in 60/95 patients (IAS: 5/10, EAS 26/41, both 24/44). There was no significant difference in the occurrence of impaired MES and the site of the sphincter defect. MES was also impaired in 27/64 patients with morphologically normal sphincter: this was not significantly from the defect group. In the defect group MES of the entire anal canal was impaired 34/45 (IAS:4/10, EAS: 15/41, both: 15/24) and in 17/63 in patients with normal sphincters. There was no significant difference between the groups. These results show that impairment of MES is common in patients with FI. However, there is no specific association with disruption of the IAS and/or EAS. These data indicate that impairment of MES is not a direct consequence of sphincter trauma.

W32

TERMINAL INTESTINAL EMPTYING: SLOWER FOR SOLIDS THAN LIQUIDS, AND INHIBITED BY A SECOND LIQUID MEAL.

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Although ileo-colonic transit of solids is known to occur episodically, little is known about the control mechanism. We hypothesised that transfer of a solid meal into the colon would be augmented by ingestion of a subsequent liquid meal.

Methods. 12 volunteers participated in a 2 part study. In part 1, 3 fasted subjects ingested 5MBq Tc99m-labelled resin baked into a pancake (400kcal) containing 15gms of bran. Serial images were obtained to determine the T50 gastric emptying (GE) and T50 colonic retrieval of the meal until then the thigh. Sensitivity was measured in the upper, middle and lower anal canal. There was a sphincter defect in 95 patients (IAS: 10, EAS: 41; both: 44). MES was impaired in 60/95 patients (IAS: 5/10, EAS 26/41, both 24/44). There was no significant difference in the occurrence of impaired MES and the site of the sphincter defect. MES was also impaired in 27/64 patients with morphologically normal sphincter: this was not significantly from the defect group. In the defect group MES of the entire anal canal was impaired 34/45 (IAS:4/10, EAS: 15/41, both: 15/24) and in 17/63 in patients with normal sphincters. There was no significant difference between the groups. These results show that impairment of MES is common in patients with FI. However, there is no specific association with disruption of the IAS and/or EAS. These data indicate that impairment of MES is not a direct consequence of sphincter trauma.

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In part 2, an identical protocol was followed, with an additional second 540kcal liquid meal (400kcal Clinifeed drink and 2 digestive biscuits) labelled with water soluble In[111]DTPA, and given 3h after the pancake. Results: (mean±SEM). GE of the pancake was similar in parts 1 and 2, T50 being 115±14 and 132±11 mins (NS). At the end of the study it was not possible to determine the T50 colonic arrival of the solid meal, as <50% of Tc99m label lay in the colon both in parts 1 and 2. A significantly smaller proportion of Tc99m label lay in the colon (11h post ingestion) in part 2 compared to part 1 (5±3% v 18±4%, p<0.05). In addition, a much higher proportion of In[111] label (92±10%) resided in the colon 3h after ingestion. Small bowel transit was significantly faster for the liquid compared to solid meal (3.6±0.4 v >9.1h, p<0.01), resulting in the liquid meal overtaking the solid meal. Conclusions: 1. Feeding the liquid meal slowed terminal ileal transit of the first. In implying that a fasting motility pattern is more effective in clearing the terminal ileum of solid residue. 2. Surprisingly, the liquid phase marker of the second meal overtook the solid phase of the first meal, implying a sieving effect of the terminal ileum with selective retention of solid residue.
Demonstration that Lactulose Increases Intracolonic Water Content, Dispersion, and Drug Absorption by Combined Colonic Echoplanar Imaging (EPI) and Scintigraphy.

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We have previously demonstrated enhanced absorption from the proximal vs distal colon. We postulated that this was due to increased proximal water content augmenting absorption by increasing mucosal contact. The aim of this study was to increase or decrease intracolonic water content using lactulose or codeine respectively, and to observe the effect on absorption. Methods: 16 volunteers were randomised to a 3 way 5 day crossover study and were treated with lactulose 20mls tds, codeine 30mg qds, or control diet alone. Epi on day 3 allowed assessment of colonic water (T1 values). Stools were also freeze-dried to assess water content. Indium labelled amebrite resin and quinine were targeted to the distal gut using a timed release delivery system. Serial scintigraphy determined release position, ascending colon transit time (ACCT), and dispersion at 3h (ave number of colonic regions of interest containing >10% of dose). Absorption was measured on a 20h urine collection. Results [mean±SEM]: Lactulose treatment caused more extensive dispersion [3.4±0.3 vs 1.6±0.2, p=0.04], an increase in free intracolonic water [T1 69±5s vs 49±4, p=0.03 one-tailed] and stool water [75±2% vs 61±2%, p<0.001], and a shortened ACCT [4.7±0.8 vs 8.9±1.8h, p<0.01] compared to codeine. Position of release of drug was similar in all 3 treatment groups. Absorption was increased by lactulose vs control (median 4.25% vs 2.60%, p=0.02). Conclusion: Lactulose enhanced drug absorption. We speculate that this is due to increased colonic water which lowers luminal viscosity, facilitating drug diffusion from lumen to mucosa.

Endoanal Ultrasonography: Can it Detect Rectoceles?

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Endoanal ultrasonography is commonly used to detect sphincter defects in patients with faecal incontinence. A rectocele is a prolapse of the rectum into the vagina and is commonly diagnosed on barium proctography or isotope defaecography. In addition to being invasive, these techniques involve administration of significant amounts of radiation. The aim of this study was to assess the efficacy of endoanal ultrasonography in diagnosing rectoceles. We performed endoanal ultrasonography (EUA) on 111 patients with a clinical diagnosis of rectocele. All patients had isotope defaecography to quantify rectal and rectocele emptying. EUA was performed using a rotating 7.5MHz ultrasound probe with the patient in the left lateral position. EUA diagnosed a rectocele in 88 of 111 patients (80%). 68 of the 88 patients diagnosed to have a rectocele on EUA had a significant rectocele (>15% isotope retention). More importantly, only 6 of 23 (25%) whose rectocele was not seen on EUA had a significant rectocele. These results were confirmed by the results of isotope defaecography. EUA was also performed in 22 patients who had undergone rectocele repair. In none of these patients a rectocele was seen on EUA. This was confirmed on subsequent isotope defaecography. This may prove to be a non-invasive way of selecting patients with rectoceles for further investigation.
Liver (clinical), and paediatrics  W39-W46

A COMPARISON OF WILSON'S DISEASE IN BRITAIN & INDIA

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Dept of Paediatrics, *Centre for Human Genetics, Children's Hospital, Sheffield, *King Edward Memorial Hospital, Pune, India.

Wilson's disease (WD) has a worldwide incidence of 1:35,000 to 1:100,000, variably presenting as either hepatic or neurologic. We compared a cohort of WD patients from Britain and India by clinical presentation, linked markers and mutations. There were 25 Caucasian British females and 43 Indian females from the Pune region. DNA was obtained by consent from parents, affected children and siblings.

Hepatic presentation of the index case occurred in 16 (64%) of the British females and 28 (65%) of the Indian females. Particular features of Indian females' cases were as early age of onset (below the age of 7 in at least 6 females), accompanied neurological symptoms (in 6 females) and Kayser-Fleischer rings, features not seen in British cases.

Haplotype analysis was performed using three linked microsatellite markers D13S314, D13S301 and D1S296 (1). Common mutation screening was performed using PCR and restriction enzyme digest (2). In British females, haplotype analysis suggested most patients were compound heterozygotes. 20 Indian haplotypes were homozygous, suggesting identical mutations. There was no common British WD haplotype, but a common haplotype (3-5-4) was on 14% of Indian WD alleles. In British females, the common mutation H1069Q was on 5 alleles (10%) and G1269R on 3 alleles (6%). These mutations were not found in any Indian case. 11027T was homozygous in 2 Indian patients.

In 27 Indian females, 45 siblings were investigated for carrier status using the linked markers. 15 were normal, 27 were carriers and 3 were found to have WD. In two cases the original diagnosis was reversed.

In conclusion, WD should be suspected earlier than 7 years of age, especially in immigrant Asian families who may be consanguineous and have a much higher carrier rate of WD mutations. DNA analysis using linked markers can offer early diagnosis where there is already an affected WD child. WD haplotypes offer clues to identifying mutations.


ANOPLASTY - AN ALTERNATIVE TREATMENT FOR CHRONIC FISSURE IN ANO

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Introduction: Anoplasty has previously been used to correct anal stenosis associated with a fissure in ano. The procedure has been extended to avoid repeated anal stretches or sphincterotomy and in other circumstances where there is a danger of incontinence.

Aims: 10 patients with chronic fissure in ano have been treated using the technique of anoplasty; these being operated under the care of one clinician.

Patients and Methods: The age of the patients ranged from 25 to 64 (mean-65.7 years), 7 male and 3 female. All the patients had chronic fissure in ano with a mean duration of symptoms of 14 months (range 6 months to 3 years). They had all had a supervised trial of conservative management. Eight of the 10 patients had had previous surgery (6-anal incontinence, 3-internal sphincterotomy). Two patients had anal stenosis. The site of the fissure was predominantly posterior.

Operative technique: The patients were operated in the prone 'jack-knife' position. The site of the chronic/recurrent fissure was superficially excised. A flap of healthy perianal skin was raised and mobilised and advanced into the anal canal and sutured in place. Seven of the 10 patients had a diamond shaped flap while the 3 had a V-V advancement. Patients were discharged from the hospital on an average in 3.8 days (range 2 to 9 days).

Results: 9 of the 10 patients in this series had symptomatic relief and complete healing of the fissure on follow up examination. The follow up period was between 2 and 10 months (mean 5 months). There was one recurrence treated by sphincterotomy. Morbidity included minimal wound infection in 2 patients and post operative urinary retention in one patient.

Conclusion: The technique of anoplasty appears to be satisfactory in the treatment of recurrent chronic anal fissures without iatrogenic damage to the sphincter mechanism. We feel that it may well have a role to play as the primary surgical procedure of choice in patients who are not relieved by conservative management and where there is a danger of precipitating incontinence.

DISTRIBUTION OF INTERSTITIAL CELLS OF CAJAL (ICC) IN THE HUMAN ANORECTUM, A COMPARISON WITH THE HUMAN COLON.

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Aim: The interstitial cells of Cajal have a proposed role in the control of gut motility. The aim of this study was to establish the normal pattern of distribution of ICC in the human anorectum and compare it to the human colon.

Methods: ICC express the proto-oncogene c-kit, a cell surface tyrosine kinase receptor. ICC were identified in the anorectum and colon by immunohistochemical staining, using a rabbit polyclonal anti-c-kit antibody (Oncogene Science). Normal anorectal or colonic tissue was defined as non-involved tissue obtained at surgical resection for a non-obstructing carcinoma of the rectum or colon. 40 colonic and 25 anorectal tissue blocks were studied.

Results: In the rectum, the greatest density of ICC was observed in the muscular layers. In the longitudinal and circular muscle layers ICC were seen in the muscle bulk and in association with penetrating blood vessels. The ICC were mainly in parallel orientation with the muscle fibres, but dendritic processes did ramify between the muscle fibres more frequently than that observed in the colon. In the intermuscular plane ICC ensheathed the myenteric plexus, but less densely than in the colon. At the inner margin of the circular muscle, ICC lined the muscle layer and were also found in association with neural elements of the submucous plexus. Within the internal anal sphincter ICC were infrequent, being sparsely scattered among the muscle fibres.

Conclusion: ICC are present in the human anorectum, their pattern of distribution differs to that seen in the colon, the highest density of ICC being in the muscular layers rather than in the intermuscular plane. In the rectum the distribution of ICC would suggest a role in the generation and co-ordination of muscular activity.

HYPERFERRITINAEMIA WITH CATARACTS: A NEW HEREDITARY CONDITION

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Ferritin, the main intracellular iron storage protein, consists of two chains, a heavy (21Kda), and a light (19Kda). Ferritin synthesis is controlled at the level of mRNA translation by an iron responsive mechanism, and reflects the intracellular iron concentration. This control process depends on a highly conserved motif at the 5' non coding region of the ferritin mRNA. The only familial condition associated with hyperferritinemia is genetic haemochromatosis.

We present the first kindred in the UK in which there is a familial association between early onset cataracts and hyperferritinemia in the absence of an acute phase response.

The ferritin level in affected family members is independent of iron status. 13 members of a family were investigated after the detection of hyperferritinemia in the proband. 6 members from 3 generations had ferritin levels in excess of 800μg/dl, despite normal iron and transferrin saturations, and plasma viscosities. A liver biopsy from one patient demonstrated no excess stainable iron. Phlebotomy resulting in biochemical iron deficiency had no effect on ferritin levels. All 6 with raised ferritin levels had natural iron excretions on all iron examinations of their lens. The other family members had a normal ophthalmic examination. Direct cycle sequencing of PCR-amplified DNA from the 5' end of the L-ferritin gene on chromosome 19 revealed a T to C mutation in the iron responsive element that was only present in affected family members.

This represents the first described mutation in an Iron Responsive Element in the U.K. The description of this new autosomal dominant genetic condition has wide implications for the use of ferritin as a marker of iron overload in the screening and treatment of patients with haemochromatosis.