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THE MACROLIDE GASTROKINETIC (GK) AGENT, ABT-229, HAS AN ADVERSE EFFECT ON POSTPRANDIAL DYSPEPTIC SYMPTOMS IN PATIENTS WITH INSULIN-DEPENDENT DIABETES (DM).

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Background: GK agents like cisapride have been shown to alleviate dyspeptic symptoms associated with DM. ABT-229 accelerates gastric emptying (GE) of a solid meal in healthy volunteers, and is devoid of tachyphylaxis[1]. Macrolides have been shown to impair fundic relaxation, however, which may cause dyspeptic symptoms. Aim: to assess efficacy and safety of 4 doses of ABT-229, compared to placebo (PL) for the treatment of postprandial (PP) dyspeptic symptoms in Type I DM. Method: 270 pats were randomized DB to: 1.25 mg, 2.5 mg, 5.0 mg, 10.0 mg ABT-229 or PL, BID, 4 weeks. Pats had evidence of $\geq$ 1 PP upper abdominal symptom(s) on at least 6/14 days. History $\geq$ 3 mos, endoscopy neg; total Upper Abdominal Discomfort VAS Score (UADS) $\geq$ 150 (max: 800), PP fullness severity $\geq$ 30 (max: 100) to qualify. GE of a 420 kCal solid meal measured (^{13}C-OBT) for *a priori* stratification into delayed (30%) and normal GE (70%). History of PUD or IBS excluded. Results: For UADS, the mean % changes from baseline (BL) were 43, 34, 45, 37 and 39 for PL, 1.25, 2.5, 5.0, 10.0 mg ABT-229 BID resp. Results for individual symptoms' severity, frequency, bothersomeness, showed ABT-229 and PL to be indistinguishable ($p>0.05$), but suggested an inverse dose-response relationship. Severity of bloating, epigastric pain, PP nausea, heartburn, regurgitation worsened dose-dependently in greater N° of pats receiving ABT-229 than PL ($p<0.05$-0.10 for 10 mg). Bothersomeness indices indicated a similar trend. GE status had no effect on outcome. Daily diary entries for PP fullness, epigastric bloating, epigastric discomfort and PP nausea similarly suggested an inverse dose-response relationship for improvement of fou 24 dyspepsia, with the sum of scores decreasing with: 42%, 30%, 36%, 35% and 26% over BL for PL, 1.25, 2.50, 5.0, 10.0 mg ABT-229 BID, respectively ($p<0.05$; 10 mg). Epigastric discomfort diary scores were sign ($p<0.05$) worse for 10 mg ABT-229 than for PL. Similarly, for PP fullness, improvement was sign smaller for 10 mg ABT-229 than for PL ($p<0.05$). ABT-229 appeared safe and well-tolerated. No QT_C prolongation was observed. Conclusion: a) Macrolide GKs did not relieve dyspeptic symptoms in Type I DM; rather they improved less than with PL; b) overall GE acceleration is not at the root of symptom improvement observed with some GK drugs; c) fundic accommodation and emptying, and decreasing sensory thresholds to distension may be more important targets for future therapy. Ref: 1) M. Verlinden et al. Gastroenterol. 1997;112(4):A846.

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ALOSETRON RETARDS SMALL BOWEL AND OVERALL COLONIC TRANSIT IN DIARRHEA-PREDOMINANT IRRITABLE BOWEL SYNDROME (D-IBS).

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Alosetron, a potent and selective 5-HT_3 receptor antagonist, relieves abdominal pain and improves bowel function in females with D-IBS (GE 116:A1036, 1999). Aim: To assess effects of alosetron on GI and colonic transit in D-IBS male and female patients. Methods: In an open trial of alosetron 1 mg bid for 6 wk, we measured GI and colonic transit before and during final 2 days of treatment. Patients fulfilled Rome I IBS criteria and reported D-IBS for at least 1 year. Transit was measured by scintigraphy using a ^{99m}Tc-egg and a delayed release capsule for colonic delivery of ^{111}In-charcoal. Gastric emptying (GE) at 2 and 4 hr and colonic filling at 6 hr were estimated. Colonic transit was assessed as geometric center (GC=weighted average of counts in 4 colonic regions and stool, range 0-5) at specified times and ascending colon (AC) emptying t1/2. Normal or fast colonic transit at the pretreatment test (GC of $\geq$2.65 at 24 or $\geq$3.89 at 48 hr) was required to continue the study, which requires 30 patients; to date, 22 have entered, and 15 (8M, 7F; mean age 43 yr, range 18-66 yr) completed the study. Transit parameters pre- and post-alosetron were compared by paired t-tests. Results: Pretreatment transit was not significantly different in male and female D-IBS except for GE at 2 hr (male 67±4%, female 49±6%; $p<0.05$). Alosetron did not affect gastric emptying, but retarded small bowel, overall and proximal colonic transit (mean±SEM, table). The change (pre-post) in the primary study endpoint, GC 24 hr, was -0.07±0.3 in men and -1.29±0.4 in women ($p<0.05$ on 2-sample t-test). Conclusion: Alosetron retards small bowel, overall and proximal colonic transit in D-IBS patients. In this preliminary sample, greater effects on colonic transit were observed in females with D-IBS. Study S3B10906 supported by Glaxo Wellcome.

	Pre-alosetron	Post-alosetron	p
Colonic filling 6hr(%)	73±6	50±10	0.03
Colonic GC 8hr	2.7±0.4	1.3±0.2	0.001
Colonic GC 24hr	4.0±0.3	3.4±0.3	0.04
Colonic GC 32hr	4.5±0.2	3.8±0.3	0.02
Colonic GC 48hr	4.9±0.1	4.2±0.3	0.03
AC t1/2 (hr)	7.9±1.4	14.2±2.5	0.03

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DO OSMOTIC LAXATIVES ACTIVATE THE ILEOCOLONIC BRAKE ?

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Alterations in gastrointestinal motility and hormone secretion that are observed in malabsorption syndromes have been related to activation of the ileocolonic brake. Aim of the present study was to investigate in healthy volunteers whether the osmotic laxative magnesiumsulphate ($MgSO_4$) affects gastrointestinal and gallbladder motility and gut hormone secretion and is associated with activation of the ileal brake. Methods: Eight healthy volunteers (4F, 4M; age 17-24 yr) were studied on four separate occasions for 360 min: 1) after meal stimulation (800 kcal) combined with either oral $MgSO_4$ (15 g in 50 ml water) or 2) placebo; and 3) during fasting combined with either oral $MgSO_4$ or 4) placebo. Antroduodenojejunal motility (perfusion manometry), duodenocaecal transit time (DCTT, lactulose H_2 breath test) and gallbladder motility (ultrasonography) were recorded. At regular intervals blood samples were drawn for determination of plasma CCK and PYY (RIA). Results: $MgSO_4$ significantly ($p=0.01$) accelerated DCTT from 65±8 to 40±6 min while fasting and from 54±7 to 31±3 min postprandially. $MgSO_4$ did not significantly influence MMC cycle length: 99±13 versus 101±9 min. After meal ingestion the reoccurrence of phase III (duration of fed pattern) was not affected: $MgSO_4$ 281±46min versus placebo 307±31 min. Postprandial gallbladder emptying was significantly ($p<0.05$) reduced after $MgSO_4$ compared to placebo (40±8% vs 60±6%) despite increased postprandial CCK secretion:206±69 ($MgSO_4$ + meal) vs 95±43pM.360 min (placebo + meal). On the other hand postprandial plasma PYY levels were significantly increased after $MgSO_4$ compared to placebo (1667±395 vs 545±125 pM.360 min). Conclusion: The osmotic laxative $MgSO_4$ accelerates intestinal transit both in the fasting and fed state but does not significantly affect antroduodenojejunal motility. Only in the fed state $MgSO_4$ activates the ileal brake with PYY release and inhibition of gallbladder emptying.

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SACRAL NERVE STIMULATION FOR IDIOPATHIC SLOW TRANSIT CONSTIPATION.

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PURPOSE: Some patients with idiopathic slow transit constipation are unresponsive to conservative treatments, while colectomy has a variable and poorly predictable outcome. Sacral nerve stimulation is a less invasive and reversible procedure which enables direct neuromodulation of the pelvic floor and hindgut. It has been used successfully in the treatment of urological disorders and faecal incontinence, and some of these patients with concurrent constipation have also noted improved stool frequency and rectal evacuation. This study aimed to assess the clinical and physiological effect of continuous sacral nerve stimulation in patients with idiopathic slow transit constipation. METHODS: Eight women (median age 47 years, median symptom duration 31 years, median stool frequency once per 6 days) were implanted with a temporary percutaneous stimulating S3 electrode for 3 weeks. A bowel symptom diary card, anorectal physiological studies, and a radio-opaque marker transit study were completed before and during stimulation. RESULTS: Two patients had cessation or marked diminution of symptoms, including normalisation of bowel frequency. Colonic transit did not return to normal in any patient. Rectal sensory threshold to distension was decreased during stimulation. CONCLUSIONS: Percutaneous temporary sacral nerve stimulation symptomatically improved a minority of patients with resistant idiopathic slow transit constipation. Sensory function was altered by stimulation. Further studies are required to identify patients who may benefit and to assess a range of stimulation parameters. *Dr Paul Wiesel is supported by a grant from the Swiss Spinal Cord Injury Society*