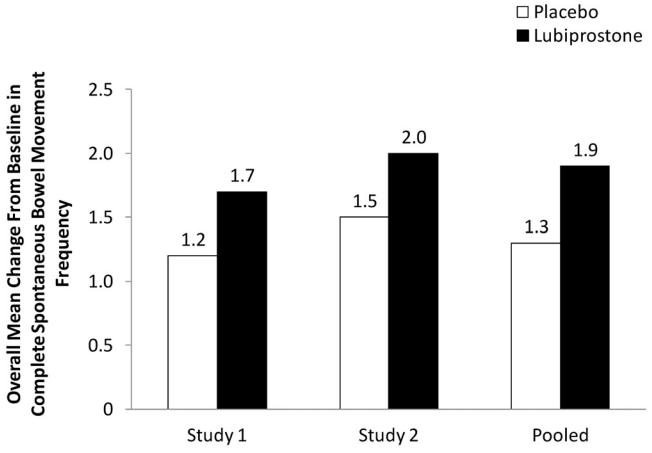
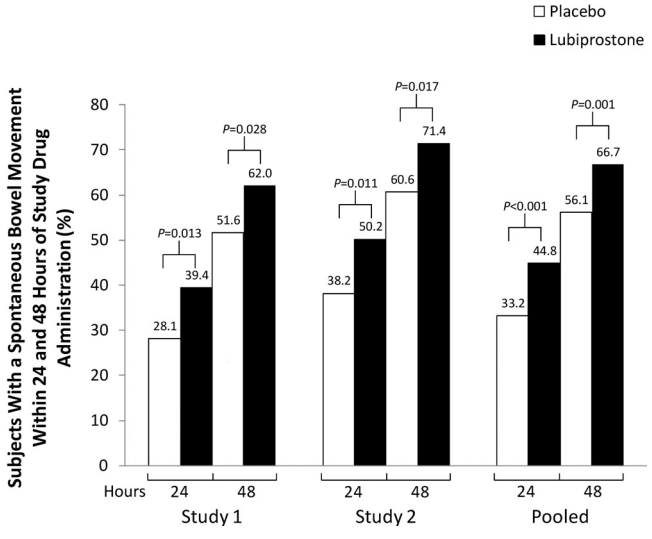


Su2042

Time to Onset of Lubiprostone Treatment Effect in Chronic Non-Cancer Pain Patients With Opioid-Induced Constipation: Data From Two Phase 3, Randomized, Double-Blind, Placebo-Controlled Trials

Taryn Joswick, Shadreck M. Mareya, Peter Lichtlen, Fasil Woldegeorgis, Ryuji Ueno

Background: Opioids are often used to manage chronic pain, yet no orally administered medications are currently indicated for opioid-induced constipation (OIC), an adverse effect commonly associated with these pain therapies. Recently, 2 multicenter, phase 3 trials (NCT00595946 [study 1] and NCT01298219 [study 2]) evaluated the efficacy and safety of oral lubiprostone for relieving symptoms of OIC in patients with chronic non-cancer pain. Because predictable relief of constipation following initiation of therapy is important for the successful treatment of OIC, the time to onset of a patient's first spontaneous BM (SBM) after starting treatment was analyzed for each trial and as an integrated analysis of combined data from both studies. **Methods:** Adults on chronic opioid therapy with OIC, defined as <3 SBMs per week, were randomized to receive lubiprostone 24 mcg or placebo in a double-blind fashion twice daily for 12 weeks. An SBM was defined as a BM for which no use of a rescue medication (eg, laxative or stool softener) had occurred in the previous 24 hours. Proportions and median times to onset of a patient's first SBM were estimated using Kaplan-Meier methods in a time-to-event analysis. Patients with no SBMs were censored and their time to first SBM was set to the full study duration. **Results:** The efficacy (intent-to-treat) populations included 438 patients (lubiprostone, n=221; placebo, n=217) in study 1 and 439 patients (lubiprostone, n=219; placebo, n=220) in study 2; the pooled population included 877 patients (lubiprostone, n=440; placebo, n=437). Most patients were female (63.4%) and white (80.2%). Median time to SBM onset was significantly shorter in the lubiprostone group compared with the placebo group, respectively, for study 1 (28.0 vs 46.0 hours; *P*=0.030), study 2 (23.8 vs 38.2 hours; *P*=0.013), and for pooled data (26.0 vs 39.8 hours; *P*=0.001). In the individual studies and the pooled analysis, the proportion of lubiprostone-treated patients reporting their first SBM within 4, 8, 12, 24, and 48 hours after the first dose of study drug was significantly greater (all *P*≤0.028) than the percentage of placebo-treated patients reporting first SBM in the same timeframe (4 hours [14.9% vs 9.7%; 13.7% vs 5.0%; 14.3% vs 7.3%], 8 hours [23.5% vs 15.2%; 16.4% vs 8.6%; 20.0% vs 11.9%], and 12 hours [31.2% vs 19.4%; 23.3% vs 14.1%; 27.3% vs 16.7%]), with the exception of patients in study 1 at 4 hours (*P*=0.093). **Figure 1** shows the proportion of patients reporting first SBM within 24 and 48 hours in each study and overall, with all statistical comparisons achieving significance. **Conclusion:** An integrated analysis of pooled data from 2 randomized, double-blind, placebo-controlled studies confirmed the efficacy of lubiprostone in decreasing the time to onset of the first SBM in OIC patients receiving opioid therapy for chronic non-cancer pain.



Su2043

Significant Increase of Mucus and Mucin Secretion During Administration of Lubiprostone in Patients With Chronic Constipation: Its Potential Clinical Implication.

Marek Majewski, Irene Sarosiek, Grzegorz Wallner, Jerzy Sarosiek

The alimentary tract mucosa has the capacity to continuously release mucus-rich secretion with mucin as its major component, thus generating protective mucus-buffer layer covering epithelium ***(T, Jaworski, I. Sarosiek et al, DD&S, 50:357-65, 2005)*** . Mucin-driven viscosity of the alimentary tract secretion facilities greatly lubrication for continuously propagated food particles. Lubiprostone, a new ClC-2 stimulator, is well known for its great efficacy in symptom improvement among patients with chronic constipation (CC). Its impact, however, on the potential increase of lubrication through ClC-2 driven stimulation of mucus and mucin secretion remains to be explored. **The Aim:** To test the rate of mucus and mucin secretion during administration of lubiprostone and placebo in patients with CC as well as controls (CTR). **Subjects & Methods:** The study was approved by IRB and conducted in 20 patients (17F, mean age of 37) with symptoms of CC, diagnosed acc. to Rome III criteria, and 20 CTR (13F, mean age of 42). Patients with CC and CTR were randomized to 1 week of therapy with lubiprostone (24 mcg BID) or placebo in a double blind, cross-over designed study. The contents of mucus and mucin were assessed in gastric juice collected in basal and pentagastrin (PG)-stimulated (6µg/kg b.wt. s.c.) conditions. Mucus content was measured gravimetrically after dialysis and lyophilization of gastric juice, whereas mucin content was measured after its purification using CsCl density gradient ultracentrifugation (260,000 g for 48 hrs). Results are presented as Mean ±SEM. Statistical analysis was run using **Σ**-Stat. **Results:** In patients with CC the rate of gastric mucus secretion during therapy with lubiprostone was 95% higher (260 ±29 vs. 133 ±16 mg/hr, P=0.001) in basal and 24% higher (341 ±49 vs. 276 ±20 mg/hr, P=0.230) in PG-stimulated conditions than after placebo. In patients with CC the rate of gastric mucin secretion during lubiprostone therapy was 85% higher (99.4 ±14 vs. 53.6 ±7 mg/hr, P=0.011) in basal and 38% higher (101 ±17 vs. 73 ±9, P=0.162) in PG -stimulated conditions than after placebo. In CTR, the rate of gastric mucus secretion during lubiprostone therapy increased 42% during basal (NS) and increased 20% (NS) in PG -stimulated conditions vs. placebo. The rate gastric mucin secretion in CTR during lubiprostone therapy was 45% higher (NS) in basal and was 28% higher (NS) in PG -stimulated conditions vs. placebo. **Conclusions:** 1.The significantly higher content of gastric mucus and mucin during therapy with lubiprostone in patients with CC may imply a potential role of ClC-2 stimulation in mucus and mucin secretion. 2. This novel effect of lubiprostone may contribute to augmented lubrication and accelerated colonic transit, thus relieving symptoms in patients with CC and potentially expanding further a new therapeutic avenue in the future.

Su2044

Mesalamine Improve Symptoms of Diarrhea-Predominant Irritable Bowel Syndrome

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Background: Studies demonstrated that some Irritable Bowell Syndrome (IBS) patients display persistent signs of minor mucosal inflammation with ativated T lymphocytes, mast cells and enhanced expression of proinflammatory cytoquines. Mesalazine has intestinal anti-inflammatory properties and has been indicated for inflammatory bowell disease. Preliminary reports showed benefits after Mesalamine treatment on diarrhea-predominant IBS(IBS-d) but stronger evidence with placebo controlled studies are lacking. Aims : Evaluate the effects of Mesalamine therapy on symptoms of IBS-d patients. Methods: Based on Rome III criteria, 21 IBS-d patients (18 year or more) were selected after sign an informed consent. To exclude organic diseases all patients underwent colonoscopy, stool culture, serum anti-endomisium antibody, lactose tolerance test and ova and parasite stool exam. Drugs that might have any effect on intestinal motility or secretion were not allowed. At baseline (pre-treatment) all patients answered a 4 likert scale protocol including: stool frequency, stool form and consistency (Bristol scale), abdominal pain and distension. Patients were divided in 3 groups: Groups 1 and 2 were randomized and Group 3 Open Label: 1 - Placebo Group (PG) - 7 patients received placebo t.i.d. for 90 days 2 - Mesalamine Group (MG) - 7 Patients received Mesalamine 800mg t.i.d. for 90 days. 3 - Mesalamine Open Label Group (MOLG) -7 Patients received Mesalamine 800mg t.i.d. for 90 days. Monthly clinical visits were made and at the end of 90 days they answered again the symptom score protocol.(Max. score = 16, min score = 4). Paired t test was used for statistical analyses. Results: Compared to baseline, there were statistically significant reduction of symptom score at 90th day therapy in MG (M[SD] x M[SD]) 12,50[3,21]x4,33[0,52]p=0.001 and in MOLG 10,71[0,49] x 4,57[0,79]p=0.0001.No statistically significant results were seen in PG. Statistically significant results were seen when compared PG and MG 8,83[3,82]x4,33[0.52]p=0.04 and PG and MOLG p=0.01.There were no statistically significant differences between MG and MOLG p=0.51. Conclusion: Mesalamine improved the Key symptoms in IBS-d patients. These results warrant further larger studies.

Su2045

Characterization of Excitatory and Inhibitory Neuromuscolar Pathways Regulating Colonic Motility in a Rat Model of Parkinson's Disease

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Introduction. Parkinson's disease (PD) is characterized by degeneration of nigrostriatal dopaminergic neurons. Patients with PD can develop gastrointestinal motor dysfunctions, and alterations of their enteric nervous system have been also observed. This study examined the patterns of colonic neuromuscular excitatory and inhibitory pathways in a rat model of PD. Methods. PD was induced in rats by intra-nigral injection of 6-hydroxydopamine (6-OHDA). Animals were sacrificed 28 or 56 days after surgery. Colonic circular muscle preparations were set up in organ baths with Krebs solution, and connected to isometric transducers to record contractions (g/g tissue) elicited by electrical stimulation (ES, 10 Hz),