Tu1436

Daikenchuto (DKT), a Japanese Traditional Herbal Medicine Ameliorated Gastrointestinal Hypermotility by Downregulated the Interleukin-17A in a Murine Functional Gastrointestinal Disorder Model

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Background and Aim: Intestinal inflammation and immune activation are accompanied by alteration of gastrointestinal motility associated with alteration of smooth muscle function. We have previously reported that IL-17A directly enhanced gastrointestinal transit and small intestinal smooth muscle contraction. We evaluated the effects of daikenchuto (DKT) on the hypermotility of gastrointestinal transit persisting after acute inflammation induced by a T-cell-activating anti-CD3 antibody (αCD3). DKT is a pharmaceutical grade ethical drug widely prescribed for patients with functional gastrointestinal disorders like irritable bowel syndrome or postoperative ileus in Japan. Methods: Wild type or IL17A KO BALB/c mice were injected with αCD3 (12.5mg, i.p.), and DKT (2700 mg/kg) was administered orally once daily for 1 week. The gastrointestinal motility was evaluated by using geometric center analysis. For estimation of gastrointestinal transit, mice were orally administered with 200 μL of fluorescein-labelled dextran of 70,000 MW and the gastrointestinal tract was excised after 30 min. Fluorescence was visualized and quantified using the G-box system and the geometric center was calculated using the formula. The histology, geometric center and mRNA/protein expressions of small intestine were evaluated on days 1, 3, and 7 after αCD3 injection from mice. Results: The small intestinal tissue damage in the early phase (1- 3 days after αCD3 injection) is characterized by enterocyte apoptosis, epithelial damage and villous atrophy which had recovered by day 7 in terms of histology. However, aCD3-treated mice on day 1 (the inflammatory phase) showed hypomotility ($p<0.01$), but then displayed hypermotility on day 7 in the recovery phase ($p<0.05$). Prolonged upregulation of IL-17A was prominent ($p<0.05$) and IL-17A injection directly enhanced gastrointestinal transit ($p<0.05$). In IL-17A KO mice, while the hypomotility of gastrointestinal transit in the inflammatory phase was shown ($p<0.05$), the hypermotility in the recovery phase was not observed. There were no apparent difference in the enteropathy of small intestine between wild-type and IL-17A KO mice. DKT inhibited the immune cell infiltration and downregulated the IL-17A protein in the intestine induced by αCD3 ($p<0.05$). DKT ameliorated the αCD3-induced gastrointestinal hypermotility on day 7 in the recovery phase ($p<0.05$). Conclusions: DKT ameliorated the hypermotility of gastrointestinal transit by downregulated the IL-17A. DKT may lead to the development of new pharmacotherapeutic strategies aimed at a wide variety of functional gastrointestinal disorders.

Tu1437

Inflammatory Responses Associated With Postoperative Ileus Contribute to Anastomotic Leakage - A Post-Hoc Analysis of a Prospective Randomized Controlled Trial

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Background: Anastomotic leakage (AL) following abdominal surgery is a critical determinant of postoperative recovery. The etiology of AL is largely unknown. Interestingly, interventions such as chewing gum and early enteral nutrition, aimed at reducing the inflammatory response and postoperative ileus (POI) also have a beneficial effect on AL co-occurrence. The aim of this study was to investigate the relation of POI with inflammation and AL after colorectal surgery. **Methods**: A post-hoc analysis of a prospective randomized controlled trial, in which patients underwent colorectal surgery, is performed. Patients were stratified for POI versus no POI, aimed at investigating AL and inflammation. Clinical parameters were prospectively registered in a database. I-FABP (marker for tissue damage) and the inflammatory response in plasma and colon tissue were determined. **Results**: AL was present in 9 of 43 patients in the POI group, and in 1 of 65 patients in the group without POI ($p<0.001$). We found a significant association between POI and AL (OR 12.57, 95% ci 2.73 to 120.65; P=0.0005). Patients with POI had significantly higher plasma levels of soluble tumor necrosis factor receptor 1 (TNFRSF1A) at 4 hours postoperatively than patients without POI: respectively 0.89 (IQR 0.56) versus 0.80 (IQR 0.37) ng/l (P=0.04) and higher plasma levels of CRP on the second day postoperatively: respectively 234 ± 77 versus 163 ± 86 mg/l (P=0.001). Patients who developed AL had significantly higher plasma levels of I-FABP compared to patients without AL at 24 hours after onset of surgery. **Conclusion:** our data indicate that the occurrence of POI and AL are correlated as patients with POI and an increased inflammatory response, show a higher prevalence of AL.

Tu1438

Avoiding Allergens Associated With Food-Related Type 4 Hypersensitivity Reactions Improves Symptoms of Irritable Bowel Syndrome

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Background: Irritable Bowel Syndrome (IBS) is a functional gastrointestinal disorder characterized by abdominal pain or discomfort coinciding with altered stool form or frequency. Recent developments in the pathophysiology of IBS point to various causes for the symptoms, including certain food triggers. To date, however, food allergy largely has been refuted. Food related type 4 hypersensitivity reactions may contribute to the pathogenesis of IBS and IBS-like symptoms. **Objective:** To evaluate if identified type 4 food allergens, when eliminated from the diet, alleviate symptoms of IBS, suggesting that the etiology of symptoms in some cases is a newly described disease, allergic contact enteritis (ACE). **Methods:** Patients with physician-diagnosed IBS or who met the Rome III criteria were eligible for study participation and were self-referred. Skin patch testing was initiated using an extensive panel of type 4 food allergens (118 to 122) identified in the literature. Following patch test application on day 1, two follow up visits were performed on day 3 and either day 4 or 5. On day 3, patches were removed and initial results were read by a board-certified dermatologist. Final patch test reading was performed on day 4 or 5, to allow for any delayed reactions. A questionnaire was distributed at this time, to be completed and returned by the patient after one month of avoiding the identified allergens. This questionnaire asked the patient to report their baseline IBS symptoms as well as how they changed after one month of food avoidance. **Results:** Thirty-nine patients were included in this study. Average age was 43 +/- 17 years and 76.9% were female. Subcategories of IBS included 44% diarrhea predominant, 18% constipation predominant, 28% mixed, and 10% unknown. Common allergens which showed a response included cinnamon bark, horseradish, sodium bisulfite, carmine, benzoyl peroxide and octyl gallate. Initial score on the 10 point questionnaire was 6.36 +/- 2.5 for abdominal pain/discomfort. We found statistically significant improvements in the severity of abdominal pain by 4.22 +/- 2.7 points ($p<0.001$) and IBS symptoms by 5.44 +/- 3.3 points ($p<0.001$), all after one month of food avoidance. Overall, 85% of patients had some or total improvement in their global IBS symptoms and 87% had some or total improvement in abdominal pain/discomfort alone. **Conclusion:** In this introductory study, our results show that 85% of patients with IBS had some or complete improvement with avoidance of known type 4 food allergens identified by skin patch testing. This raises questions about a possible overlap between IBS and allergic contact enteritis. Larger studies will be needed to investigate dose-related response and to more fully address the placebo effect.

Tu1439

The Biomechanical Influence of Intestinal Gas and Chyme on Small Bowel Peristalsis

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Background: The small intestine plays a critical role in processes such as digestion by serving as both a mixer and bioreactor. Like the heart, intestinal muscles generate their own intrinsic rhythm for peristalsis and these complex motions contribute to normal and pathologic states such as ileus. Much of the previous work on intestinal motion has been limited to electrophysiologic studies and the application of biomechanical modeling to intestinal motion has not been performed before. **Objective:** To determine the kinematics of intestinal motion and the *in vivo* contribution of gas and chyme to small bowel function in animal models. **Methods:** Male Sprague Dawley rats (characteristic weight 350g) are housed in the reversed cycle 7 days before terminal surgery. We apply Fentanyl/Droperidol intramuscular injection which has minimum effects of anesthesia on intestinal contractility[1]. After anesthesia, a midline incision is made in the rat. Loops of small intestine are confined by pins in albumin-physiological salt solution bath at 37 °C . We film the motion of intestine by high-definition camera (Sony HDR-XR200). We visualize the context of chyme by microfluoroscopy (6C beam line of a Pohang Light Source PLS-II, Korea). **Results:** A full-length segment of small intestine was isolated and studied using high-definition analysis. From stomach to cecum, the contraction frequency was found to increase in three folds with 80% decrease in amplitude as chyme moved distally. The radial contraction frequency f (Hz) and amplitude A (cm) of the small intestine were found to be a function of distance from the pylorus s (cm) ($f = 0.01s + 0.008$, $A = -0.03s + 0.2$, $R^2 = 0.6$). The gas fraction of chyme increased from 0% in the proximal small intestine to 90% in the distal portion. The gas bubbles were smaller in size and more round-shaped in the proximal small bowel as compared to the large and more irregular shaped bubbles in the terminal ileum. Figure 1.) A 350g-rat intestinal loop with pins filmed at 37°C albumin-physiology salt solution bath *in vivo*. Figure 2.) Radial contraction of small intestine as function of distance from pylorus. **Conclusion:** Intestinal peristalsis has unique biomechanical properties which are influenced by luminal gas and chyme. Gas appears to decrease the effective cross-sectional area of the small intestine with increased frequency, but decreased intensity, of contractions. These changes in biomechanics may contribute to dysfunctional states such as ileus. **Reference:** Dixon, *et al*. *Microcirculation*, 2006

Figure 1.

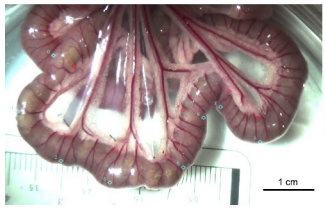
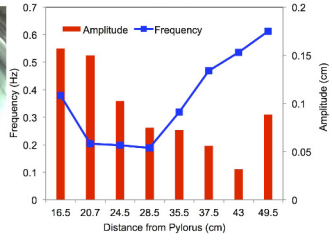


Figure 2.



Tu1440

Methane Production Is Associated With Delayed Small Bowel Transit on Wireless Motility Capsule Testing

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Methane presence on breath testing has been associated with a constipation phenotype as well as delayed colonic and orocecal transit times, but its relationship to small bowel transit time (SBTT) has not been clearly established. We performed a retrospective analysis of all patients who underwent Smartpill wireless motility capsule (WMC) testing and lactulose breath testing between January and October 2015. The area under the curve for methane was calculated at 90 minutes (methane 90) and for the total duration of the lactulose breath test, 180 minutes (methane total). Pearson's correlation coefficients were generated for methane AUC and gastric, small bowel, colon, and whole gut transit times. 29 patients underwent wireless motility capsule testing, 21 (72%) were female and mean age was 49 years. Indications for WMC testing included nausea and vomiting (48%), constipation (45%), gastroparesis (24%), and bloating (14%). Delayed SBTT was found in 5 subjects (17%), and delayed CTT in 9 subjects (31%). SIBO was diagnosed in 6 subjects (21%). Methane Total had modest correlation with SBTT (r = 0.11). Using a methane total cutoff of 975 ppm, and a methane 90 cutoff of 465 ppm to predict delayed SBTT, yielded a sensitivity of 33% and a specificity of 100%. One patient with extremely high methane total (1755 ppm) and