

Motility Disorders: Top to Bottom

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Good morning, everyone. I'm Henry Parkman, the Director of the GI Motility Laboratory at Temple University Hospital in Philadelphia, PA. If you look at the number of reasons why people come to see doctors, GI motility disorders and functional bowel disorders are actually the most common disorders. I chose the first 12 abstracts that I found the most interesting. The second 12 are for your additional review.

This session is entitled Motility Disorders from Top to Bottom, so I started at the top.

Abstract 211853: "Life expectancy, complications and causes of death in patients with achalasia: Results of a 33-year prospective follow-up investigation"

This is by Dr. Eckhardt's group. He has written several articles in *Gastroenterology* about his experience with achalasia. In this abstract, he reports on his patients with achalasia in a defined database. He enters them in the database at diagnosis and follows them every two years with his own symptom score in which he grades dysphagia symptoms and treats them accordingly. In this series, he put in new patients from 1972-2002. He had 178 patients, mean age 47 with newly diagnosed achalasia. He followed them until 2005. He had follow-up on 99% of the patients. That's kind of amazing to have follow-up that high. The mean follow-up was 10.5 years. Over that time, each patient had an average of 2.2 invasive procedures (range 1-13) for achalasia. He does not elaborate on what procedures were performed but the most likely included dilation, surgical myotomy and Botox injections. The mean dysphagia symptom score was initially 6; at last follow-up it was down to 1.5. So, he was able to reduce their symptoms remarkably and keep them at what I would consider a low level. Disease and therapy related complications occurred in 18.5% of the patients; megaesophagus (7%), reflux esophagus (3.3%), peptic stricture (2.2%), and large esophageal diverticuli (2.2%). Their survival rate was similar to the general population. Although the symptom score went down in the vast majority of the patients, the complications were not inconsequential. Reflux esophagitis and peptic stricture are complications that usually occur after Heller myotomy and less with dilatation. Megaesophagus usually occurs in untreated disease so perhaps some of these were undertreated. Following the patients every two years, they were able to effectively reduce their symptoms and their survival rate was similar to that in the general population, despite complications. The causes of death were similar to the normal population with the exception of an increased amount of pulmonary disorders. My take home message from this is with careful follow-up and appropriate treatment of these patients, their life expectancy is actually fairly normal. They are very well treated, with their mean dysphagia score fairly low. I thought this was impressive.

The increase in pulmonary related deaths is of interest. Aggressive dilatation or Botox usually does not lower the esophageal sphincter so dramatically that you increase the rates of pulmonary complications of pneumonia. One would expect that more after myotomy, if a fundoplication was not performed.

It is of interest that he did not report any esophageal carcinoma which has been described after long-standing disease. That's a somewhat controversial subject and this would suggest it is not a major risk. On the other hand, only 178 patients in 30 years is not a large number. Unfortunately, the abstract doesn't go into enough detail to answer many of our questions. There's a lot we don't know, but we can ask them about that.

Abstract 226122: "Reduction of interstitial cells of Cajal (ICC) in Auerbach's plexus in patients with achalasia: New insights in pathogenesis"

The interstitial cells of Cajal are the pacemaker cells of the GI tract. They're usually very well described in the stomach where you need the antral motility and antral contractions to help pulverize the food and push things out. They are also described well in the colon. They have not actually been well-described in the esophagus. This comes from the same group as the first abstract and looks at the lower esophageal sphincter in normal people and in patients with achalasia. In 35 patients that underwent Heller myotomy or esophageal resection, they took biopsies from the lower esophageal sphincter or the esophagectomy specimen and stained them for the neurons, interstitial cells of Cajal, as well as nitric oxide. Autopsy specimens from patients with normal esophageal function were controls. They found that nitric oxide was markedly depleted (not a new finding) and also showed that there is a decrease or absence of the interstitial cells of Cajal. The authors speculate that the pathogenesis of achalasia may be in part due to a lack of interstitial cells of Cajal in the LES.

Unfortunately, we can only get the tissue with Heller myotomy or esophageal resection. In most patients with achalasia, we do pneumatic dilation or Botox so there is no way to look at these patients nor can we know at what stage those who had Heller's were; early or late in disease. This is early data of unknown importance.

Abstract 226530: "The role of esophageal mast cells in patients with symptoms of heartburn"

Mast cells have been increasingly recognized over the last several years as a possibly important cell in GI motility and functional bowel disorders. This abstract looks at the role of the esophageal mast cells in patients with reflux disease. This is by Ann Ouyang who is at Hershey and collaborating with people from Johns Hopkins Hospital. They had 16 patients with symptoms of heartburn who were endoscoped and biopsied at the distal esophagus. Exclusion criteria included asthma, atopic skin disease, chronic inflammatory conditions, food allergies, celiac disease, steroid treatment, ischemic heart disease, or esophageal varices. They stained Mast cells and TRPV1 which is the capsaicin receptor, one of the markers that might be triggering pain. They found that the Mast cells were juxtaposed to these neurons containing the capsaicin receptors. Heartburn was scored as 0-4, 5-9, and 10-15. Mast cells were higher in the group with scores of 10-15 than 0-4 ($p < .03$). The authors raise the possibility that heartburn may be mediated by release of inflammatory mediators from the Mast cells and through this capsaicin receptor. An interesting preliminary observation, however they only biopsy the distal esophagus and do not appear to have looked at neutrophils, lymphocytes, or eosinophils. Also, what is triggering the release of the Mast cells? Is it acid or bile?

In addition, they did not do esophageal pH testing and do not comment on PPI response, so they haven't shown that these patients have acid reflux just going by symptoms. Studies have shown that we can't distinguish symptoms from non-ulcer dyspepsia, ulcer disease or functional heartburn.

The etiology of heartburn is not clear. More to do in this area.

Abstract 217002: “Chemical hypersensitivity in patients with functional dyspepsia”

This is along the same theme; asking the question, “What’s triggering symptoms in patients with functional dyspepsia?” They had healthy controls and patients with functional dyspepsia, inflammatory bowel disease, gastric ulcers and other GI symptoms. They looked at nine different symptoms before and 30 minutes after giving a 0.75 mg capsaicin capsule. They did an aggregate symptom score and compared all groups to healthy controls. Only patients with functional dyspepsia had aggregate scores higher than 2 SD above normal controls ($p < .01$). Sixty percent of the functional dyspepsia patients had an abnormal score, which they called a positive capsaicin test. They’re proposing that this might be a simple and non-invasive method to detect a subgroup of patients with functional dyspepsia with chemical hypersensitivity. Maybe targeting the vanilloid receptor type 1 (VR1) receptor that capsaicin activates might be a way to treat some of these patients with functional GI disorders.

If you go to the first abstract in the group we will not have time to discuss, there’s an interesting one by Ronnie Fass with Jay Pasricha entitled “Reduced pain perception in Barrett’s esophagus is likely due to downregulation of the TRPV1 receptors in the squamous epithelium rather than in Barrett’s mucosa itself.” I’m using this as an illustration to expand on this topic. The investigators biopsied patients with Barrett’s both in the Barrett’s and in the squamous epithelium. They looked for capsaicin receptors with the TRPV1 receptor. The reason they did this is that patients with Barrett’s actually have reduced symptoms of heartburn and it is thought that maybe Barrett’s mucosa doesn’t transmit the sensation of heartburn through squamous mucosa. They found that the number of TRPV1 receptors was reduced in the patients with Barrett’s in the squamous epithelium. They’re proposing that might be why they have less pain. It’s less activation of the squamous epithelium, its not related to Barrett’s mucosa itself. Actually, the Barrett’s mucosa had a slightly elevated number of these receptors. The reason I brought this up for your question is that it shows that these receptors, at least in the esophagus, are in the squamous mucosa.

Abstract 223415: “Gastric emptying (GE), major contributor to postprandial hyperglycemia in patients with type I diabetes mellitus (T1DM)”

Postprandial hyperglycemia is a risk factor for diabetic complications including type 1 cardiovascular disease. Amylin, a pancreatic hormone, is released postprandially and delays gastric emptying. Type I diabetics are amylin deficient. The authors hypothesized that, in the absence of neuropathy, type I diabetics have accelerated gastric emptying, that amylin substitution should delay gastric emptying in type I diabetics and reduce postprandial glucose excursions. Twelve normal controls and 12 otherwise healthy subjects with type I diabetes were treated with 30 mg pramlintide (an amylin analgesic) or placebo subcutaneously after a 472 kcal meal. Insulin was infused IV to ensure that fasting glucose levels were normal and to prevent postprandial hyperglycemia. Gastric emptying was measured in both groups by scintigraphy. The authors found that pramlintide decreased postprandial hyperglycemia significantly greater than placebo in type I diabetics and reduced postprandial hyperglycemia. This is a complicated study and done in an artificial setting (IV insulin infusion). It is counter intuitive to delay gastric emptying in diabetics, but it may be a reasonable strategy if indeed, like dumping syndrome, rapid gastric emptying contributes to hyperglycemia.

There are a couple of abstracts I want to highlight, both from the University of Texas in Galveston.

Abstract 224355: “Diabetes induces gender dependent changes in gastric neuronal nitric oxide synthase (nNOS) expression, dimerization, and function”

The authors are looking at the inhibitory neurotransmitter in the GI tract, nitric oxide. They are looking at this in a laboratory situation in diabetic rats after streptozotocin. They find that there was impairment in

the nitric oxide pathways, more so in the female rats than the male rats. Motility disorders and functional bowel disorders are more common in females than males. The reason for this is not known. I've always thought it was related to female sex hormones – estrogen and progesterone. These are inhibitory in the GI tract, but it seems to be more than that. We did a study looking at gastric emptying. Even in the early phase of the menstrual cycle when these levels would be low, they still had delayed gastric emptying. This looks at the possibility of a predisposition to females where there is an impact on the enteric nervous system in this diabetic rat model.

Abstract 224446: “Neuropathological and genomic changes in the stomach of patients with human diabetic gastroparesis”

In this study, the authors are trying to understand what causes gastroparesis by looking at the pathologic level. They had two patients and two controls. One patient had the abrupt onset of symptoms and still remained relatively well-controlled as far as her diabetes control. That patient ultimately had to go for a gastric stimulator where they did a full thickness biopsy. They had another patient who had similar symptoms, but the diabetes was a bit more out of control and elevated hemoglobin A1C was noted. This patient also had to go to surgery for implantation of the gastric stimulator and had a full thickness biopsy done. They compared the two patients and they both had a similar degree of delayed gastric emptying. They then compared the two patients' biopsy specimens and the patient with less duration of symptoms and relatively better controlled diabetes had fairly normal appearing tissue. They performed different types of stains in the other specimen from the patient with longer duration diabetes and there were marked changes in the nerve function and muscle function, as well as abnormalities in the interstitial cells of Cajal. Fibrosis was seen in the muscle layer, which actually is not well described in patients with diabetic gastroparesis. It is thought to be more of an auto vagotomy-type picture. In this patient, besides changes in the muscle layer, they found fewer nerve fibers, as you might expect, and there was also less staining for c-KIT antibody which stains for the interstitial cells of Cajal. They bring up the fact that gastroparesis is a heterogenic disorder. You can have two patients with similar abnormalities in gastric emptying, but have marked differences in the underlying pathology. One appeared relatively normal and the other showing marked changes in nerves, muscle, and interstitial cells of Cajal. Maybe understanding this, what the underlying disorder is, might help with therapy. In these two patients, there was such disparity.

Abstract 222318: “Predictive factors for clinical improvement with Enterra gastric electric stimulation treatment for refractory gastroparesis”

We have done about 80 cases of gastric stimulation at our center. When this new score for gastroparesis came out, called the Gastroparesis Symptom Index, devised by several gastroenterologists working with some epidemiologists, they found what they thought were nine symptoms and a good way to score them. That score came out about two years ago. We started grading our patients before and after placement of the gastric electric stimulation. We followed their symptoms scores both pre and post therapy and looked at a variety of factors. In this study period, we implanted 28 patients. Fourteen reported improvement, eight no change, and six got worse. We looked at a variety of factors and found three factors that seemed to impact on the response rate. One - patients with diabetic gastroparesis responded better than idiopathic gastroparesis. The etiology was important. Secondly, symptoms were important. We found that patients with nausea and vomiting responded better than patients whose predominant symptom was abdominal pain. The third factor that impacted on the response rate was the use of narcotic analgesics. Narcotic analgesics were bad prognostic factors. Patients can be on narcotic analgesics for pain from gastroparesis, but also for peripheral neuropathy and some other disorders. Regardless, they appear to decrease response to the stimulator. If they have idiopathic gastroparesis and they say pain is the main symptoms and they are on Percocet daily because of the pain, they are the patients I try to stay away from or find another way

to treat them. So, three factors that might impact the treatment response – the etiology, the main symptoms, and the use of narcotic analgesics.

Abstract 223947: “A sham-controlled study of intra-pyloric injection of Botulinum toxin in gastroparesis”

This is a Botox/sham Botox study from the Belgian group. This looks at 23 patients given Botox endoscopically into the pylorus to treat idiopathic gastroparesis. The open-label studies suggest it might be very helpful. We did an open-label study where seven out of 10 patients did well. It appears to be short lived in that if we follow those seven patients that did well, almost all of them got additional treatment with either repeat Botox, domperidone, or the gastric stimulator. We used Botox to get these refractory patients out of the hospital. This is a negative study.

In this study, each patient with gastroparesis underwent two endoscopies four weeks apart. The first one was either Botox or placebo. They then crossed over to the other injection. Interestingly, they found similar improvement in gastric emptying and in symptoms with the placebo and with Botox. These authors conclude in their final sentence “In a cohort of gastroparesis patients of predominantly idiopathic origin, intra-pyloric injection of botulinum toxin does not seem superior to placebo in improving symptoms and solid or liquid gastric emptying rate.” This muddies the waters. Why are these patients getting better? This doesn’t answer the question and I think we need more studies in this area. In the group that improved with placebo, they also improved more with the second injection of Botox. The patients with the Botox initially got better with the Botox but didn’t improve with the placebo, so it is not all cut and dry. In fact, there was a placebo response that almost prevents you from interpreting the Botox response. We are doing a placebo-controlled trial at our center. In two years we have 32 patients enrolled and we have stopped. We are now waiting for the three-month response rate. This study reminds us of the fact that things can look good initially in open label studies; they don’t look quite as good as you initially thought when you do appropriate controlled trials. Unfortunately, Botox may not be that helpful in these patients.

Abstract 224572: “Tegaserod enhances gastric accommodation by antagonizing 5-HT_{2b} receptor activity in the gastric myenteric plexus and smooth muscle”

This study looks at tegaserod which, as you know, is a 5-HT₄ partial agonist that is approved for constipation in men and women and also for constipation-predominant irritable bowel syndrome in women. There were some abstracts last year which suggested that in addition to the 5-HT₄ agonist properties that accelerate motility, Tegaserod might also be a 5-HT_{2b} receptor antagonist. This study by Chung Owyang’s group in Michigan looks at the gastric accommodation reflex. Normally, when you eat your meal, the proximal portion of the stomach accommodates or relaxes to allow the entry of the food. Jan Tack has reported that cisapride and tegaserod can enhance this accommodation reflex and that might be one of the reasons why it may work for patients with functional dyspepsia. You might actually improve the accommodation reflex. This article in rats suggests that the effect of Tegaserod on enhancing this accommodation reflex is because Tegaserod is also a 5-HT_{2b} receptor antagonist. This is a very elegant study. The take home message is that agents may have other properties. I’m not quite sure if the 5-HT_{2B} receptor was known when Tegaserod was being looked into. About every five years there is something added to the nomenclature for the 5-HT receptor. There might be some other mechanisms of Tegaserod besides its 5-HT₄ properties. Fortunately, this is a good response because it might help patients with functional dyspepsia. Tegaserod might be a 5-HT_{2B} receptor antagonist and in the fundus it is thought that maybe these 5-HT_{2B} receptors release acetylcholine to contract the proximal portion of the stomach. If you give Tegaserod working as an antagonist, it would prevent that contraction and allow the proximal portion of the stomach to relax more and that is more of the accommodation reflex.

Abstract 222095: “Newer antiepileptic drugs for adults with cyclic vomiting syndrome (CVS): A novel approach to maintenance therapy”

This is by Ray Clouse’s group and brings to our attention that there are newer age psychotropic agents coming out. There are new anti-epileptic drugs that are available to treat seizures and are also used for migraine headaches. This looks at two of the agents, zonisamide (Zonegran[®]) and levetiracetam (Keppra[®]) that treat patients with cyclic vomiting syndrome. They found that some of these agents might also be useful. I’m still trying to get the courage to treat my patients with antidepressant agents, now I’ve got to gear up to treat patients using serotonin reuptake inhibitors. This is even a step above that. This open-label study treated 18 patients with CVS who failed tricyclics using anti-epileptic agents Zonegran (N=15) and Keppra (N=3). The results look pretty good. They actually prevent the attacks in just under half of the patients. This is not my armamentarium right now, but it shows you that these neurologic drugs may also be useful for GI disorders.

Abstract 222711: “A dose-ranging, double-blind placebo-controlled study of lubiprostone in subjects with irritable bowel syndrome and constipation (c-IBS)”

The last abstract is about lubiprostone. This was approved about a month ago to treat patients with chronic constipation. This abstract looks at patients with constipation predominant irritable bowel syndrome. It’s a little difficult to read because they have three-month follow-up and they report that in two of the three months there is an improvement in constipation, abdominal pain, and some of the other symptoms. This is an agent to look out for. You can already treat patients with chronic constipation. They found that improvement was highest with the 48 µg group – that’s 24 µg bid - the dose used to treat constipation. The adverse events and drop-out rates also increased with the increase in dose, so actually the adverse events and the efficacy go up with the higher dose. Their final conclusion is that lubiprostone is an efficacious and well-tolerated treatment for constipation predominant IBS. Dose dependent trends were observed with respect to safety and efficacy. This is another agent in our armamentarium besides what we have now – Zelnorm and other agents, to treat patients with chronic constipation.

At this time, I’d like to thank you all for attending this session. I hope you all have a good meeting.

Thank you.

Abstracts Discussed

211853: Life Expectancy, Complications and Causes of Death in Patients With Achalasia: Results of A 33-Year Prospective Follow-Up Investigation. *Volker F Eckardt, Tom Hoischen, Gudrun Bernhard*

Background and aims: Patients with achalasia often require repeated invasive therapies and may experience multiple complications related to the natural course of this disease and/or its therapy. This study determines the incidence of such complications and causes of death. In addition, survival rates were determined and compared with those obtained in an average population. Material and methods: From 1972 to 2002, 178 consecutive patients (mean age: 47.0±18.9 [mean±1SD] years, 105 males and 73 females) with newly diagnosed achalasia were admitted to this prospective investigation and followed until 2005 in two-year intervals. The diagnosis of primary achalasia was based on manometric, radiographic and endoscopic findings. Patients regularly underwent structured interviews with regard to their symptoms using a previously described symptom score (Gastroenterology 1992;103:1732) and were reinvestigated if significant changes in health status occurred. Survival rates were determined by Kaplan Meier estimates. We also generated survival data for an average but age and sex matched German population (Bundesamt für Statistik) and compared these findings with those obtained in patients with achalasia. Causes of death were determined from hospital records, informations supplied by private physicians and from death certificates. Results: Complete follow-up was obtained in 98.9% of all patients. The mean observation period was 10.5±6.5 years with a range from 2 to 33 years (in surviving patients). Within this time period, 175 patients underwent a mean of 2.2±1.8 invasive procedures (range 1 to 13). The mean symptom score was 6.0±2.2 at first presentation and 1.5±1.5 at last follow-up. Disease- and therapy-related complications occurred in 18.5% of all patients, the most common of which were megaesophagus (7.3%) followed by reflux esophagitis (3.3%), peptic stenosis (2.2%) and large esophageal diverticula (2.2%). A total of 24 patients (13.5%) had died. Causes of death were comparable to those of the control population with the exception of a higher incidence of pulmonary causes in patients with achalasia (12.5 vs. 2.6%). The estimated 10 and 20 year survival rates were similar in patients with achalasia (88% [95% CI:82-94%] and 76% [95% CI:66-85%]) and in sex and age matched controls (92% [95% CI: 87-97%] and 78% [95% CI:67-90%]). Conclusions: During the course of many years, most patients with achalasia require repeated therapies and experience a significant number of complications. However, causes of death and life expectancy do not differ significantly from those of the average population.

226530: The Role of Esophageal Mast Cells In Patients With Symptoms of Heartburn. *Shaoyong Yu, Deborah M Bethards, Allen C Myers, Ann Ouyang*

Introduction: The mast cell is known to be an important inflammatory cell in the GI tract. Our previous pre-clinical animal studies show that mast cell activation results in the release of inflammatory mediators in the esophagus with resulting stimulation of nociceptors. Our hypothesis is that heartburn may be a symptom similarly generated by the effect of mast cell activation on esophageal nociceptors in humans. Aims: To identify mast cells in the esophagus and review their correlation with symptoms of heartburn. Method: Sixteen patients were recruited from all patients who were referred for upper endoscopy. Exclusion criteria included asthma, atopic skin disease, chronic inflammatory conditions (RA, SLE), food allergies, known celiac disease, recent steroid treatment, ischemic heart disease or esophageal varices. During upper endoscopy biopsies were obtained from the lower esophagus and the mucosal appearance of the esophagus was noted and graded by the endoscopist. Mast cell tryptase staining was performed using a standard immunofluorescence method by an investigator blinded to the clinical information and the number of mast cells per mm² was calculated. The sections were also stained with antibodies to TRPV1 (capsaicin receptor) and PGP9.5. The patients' symptoms of heartburn were categorized using a scale from 1-5 for severity, duration and frequency (giving a maximal score of 15); this information was obtained by questionnaire completed prior to the procedure. Five patients had a symptom score of 0-4, one had a score between 5-9 and ten had a score between 10-15. The esophageal mast cell count was compared between patients with symptoms scores of 0-4 and those with scores of 10-15. Results: In the majority of patients no significant macroscopic esophageal mucosal change was noted on endoscopy. The number of mast cells was found to be significantly elevated in those patients with a heartburn score of 10-15 compared to those with a score of 0-4 (119.4 ± 37.8 vs 42.8 ± 19.1 cells/mm², mean ± SEM, p<0.03). The TRPV1 positive nerve fibers were identified in the esophageal mucosa in proximity to mast cells. Conclusion: In a patient population in which allergic and inflammatory conditions have been excluded there is a significant correlation between heartburn symptom score and number of mast cells in lower esophageal biopsies. We propose that mast cells release inflammatory mediators that are responsible for the development of heartburn symptoms in these patients without macroscopic esophagitis.

226122: Reduction of Interstitial Cells of Cajal (ICC) In Auerbach's Plexus In Patients With Achalasia: New Insights In Pathogenesis. *Ines Gockel, Juergen R Bohl, Volker F Eckardt, Theodor Junginger*

Background. Interstitial cells of cajal (ICC) form neuronal networks which are spread in submuscular, intramuscular and intermuscular layers of the gastrointestinal tract. They generate pacemaker potentials determinating the spontaneously electrical and mechanical activity of smooth muscle cells. There is a close relationship between the c-kit positive cajal cells and the

nitrogen monoxide (NO)-synthetasis as a neurotransmitter of nerve fibres. The aim of our study was to investigate the significance of interstitial cells of cajal in the plexus myentericus in patients with primary achalasia. Patients and methods. In 35 patients with a median age of 55 (14-78) years undergoing surgery for achalasia, staining of the cells of Auerbach's plexus was carried out. In 19 patients, biopsies were taken from the high pressure zone of the lower esophageal sphincter (LES) in the context of a Heller myotomy, whereas in 11 patients the complete esophagus was resected in patients with end-stage achalasia and a decompensated megaesophagus. The tissue samples were fixed in formalin, embedded in paraffin, and investigated microscopically. Apart from conventional staining methods, immunohistochemical examinations were carried out (n-NOS (=neuronal nitrogen monoxide synthetasis), neurofilament, smooth muscle antigen, Desmin, CD 117, S 100, B- and T-lymphocytes, and CD 68). Autopsy samples from patients with normal esophageal function served as controls. Results. The median duration of symptoms was 10 (0.5-63) years. 14 patients had undergone a pneumatic dilation previously, and 10 patients had had previous surgery at the lower esophageal sphincter. The preoperative Eckardt score was 6 (3-10). With a maximum diameter of the esophageal body of 45 (25-60) mm, the radiologically measured narrowest point at the cardia was 4.5 (1-15) mm. Esophageal manometry displayed a median LES resting pressure of 24.4 (12-115) mmHg. The present histopathological examination showed a marked reduction up to a complete absence of the ICC in the area of the high pressure zone of the esophagus. Staining with the antibody n-NOS points at a reduced neurotransmission in the LES. Conclusion. The present results suggest that in the pathogenesis of achalasia, especially in the development of the high pressure zone, the deficient or missing function of the cells of cajal play an important role. The associated reduction of the NO-synthetasis, therefore, is possibly responsible for the lack of relaxation of the LES, on account of the missing inhibitory neurotransmission. The reduction of the cajal cell-function also seems to be of relevance even if the cells of Auerbach's plexus are unscathed.

217002: Chemical Hypersensitivity In Patients With Functional Dyspepsia. *Johannes Matiasek, Lorenz Pipal, Johann Hammer*

Background: The pathophysiology of functional dyspepsia (FD) is unclear; chemical hypersensitivity might be a causing factor. Capsaicin stimulates the vanilloid receptors (VR1) on afferent neurons, that are involved in chemical nociception in the upper GI tract. **Aim:** To evaluate the sensitivity for gastric capsaicin in healthy controls and in patients with FD or other GI disorders. **Methods:** N=25 healthy controls, n=30 patients with functional dyspepsia (FD), n=17 with inflammatory bowel disease (IBD), n=10 with gastric ulcers or erosions, and n=19 with other GI symptoms swallowed a capsule after an overnight fast containing 0.75 mg capsaicin. Subjects filled out a graded questionnaire evaluating the severity of 9 different upper abdominal symptoms before and 30 minutes after capsule ingestion; an aggregate symptom score was calculated by adding all symptom scores. Data are expressed as mean \pm SEM; p-values <0.05 were considered significant. **Results:** Healthy controls had an aggregate symptom score of 6.3 \pm 2.9; the median was 6.5 (25% confidence interval: 4). The 75% confidence interval was 9 and was considered as the upper limit of normal. The FD group had a mean symptom score of 12.2 \pm 5.6 (p<0.001 vs. controls). The aggregate symptom scores in the IBD group was 3.9 \pm 4.4 (NS vs. controls, p<0.001 vs. FD), in the ulcer group was 3.3 \pm 4.3 (NS vs. controls, p<0.001 vs. FD), and in the group with other GI symptoms was 6.1 \pm 6.3 (NS vs. controls, p<0.001 vs. FD). 60.0% of the FD group had a positive capsaicin test (aggregate symptom score >9), 40.0% were negative. Among the FD group testing positive, 38.9% had pain-predominant FD, 50% discomfort-predominant dyspepsia; in 2 subjects data were missing. 33.3% of the patients with a negative capsaicin test had pain predominant FD, 50% discomfort predominant FD, in 2 subjects data were missing. **Summary:** 60% of patients with FD were hypersensitive against gastric capsaicin, independent whether the predominant symptom was pain or discomfort. **Conclusion:** Chemical hypersensitivity discriminates functional disorders from healthy controls and patients with other upper GI disorders. The capsaicin test is a simple and non invasive method to detect the subgroup of functional dyspepsia with chemical hypersensitivity. Targeting the VR1 receptor might be a therapeutic option in a large subgroup of patients with functional dyspepsia.

223415: Gastric Emptying (GE), Major Contributor To Postprandial Hyperglycemia In Patients With Type 1 Diabetes Mellitus (T1DM). *Juergen Woerle, Maximilian Albrecht, Rainer Linke, Mathias Nicolaus, Martin Storr, Joerg Limmer, Burkhard Goeke, Joerg Schirra*

Postprandial (PP) hyperglycemia has been identified as an important risk factor for cardiovascular disease. The pancreatic hormone amylin is released postprandially and delays gastric emptying. T1DM are amylin deficient. Accordingly, we hypothesised that 1) in the absence of neuropathy, T1DM have accelerated GE, 2) accelerated GE may be an important regulator of PP glycemia, 3) amylin substitution should delay GE in T1DM and reduce PP glucose excursions. **Methods:** We studied 12 healthy subjects (HS) and 12 otherwise healthy subjects with T1DM on two occasions each, after ingestion of a mixed 472 kcal meal with s.c. administration of either placebo (PBO) or the amylin analogue pramlintide (30 mcg). T1DM were infused with IV insulin to establish a fasting euglycemia of 90 mg/dl and to prevent PP hyperglycemia >180 mg/dl in order to avoid the effects of hyperglycemia on gastric emptying. Insulin was infused in an identical manner on both days. GE was determined by high-resolution scintigraphy (20 fr/min) over 330 min. **Results:** PP glucose excursions in T1DM exceeded those of HS during the first 150 min after meal ingestion (AUC 416 \pm 64 vs 307 \pm 24 mg/dl/150 min, p<0.05), and remained greater throughout, even though PP plasma insulin levels were 3-fold greater in T1DM. During this time period, GE was accelerated in T1DM (55.7 \pm 4.7 vs 41.7 \pm 4.6% emptied, p<0.05). GE was closely correlated with peak plasma glucose

excursions ($r=0.75$, $p<0.001$). *Pramlintide* delayed gastric emptying in HS (50% emptying at 225 ± 16 vs 177 ± 10 min) and T1DM (217 ± 10 vs 149 ± 10 min; both $p<0.001$). It abolished the increase in glycemia during the first 150 min in T1DM (-12 ± 56 vs 416 ± 64 mg/dl/150 min) and markedly reduced overall PP glucose excursions in both HS and T1DM compared to PBO (195 ± 21 vs 283 ± 25 and 119 ± 73 vs 389 ± 75 mg/dl/150 min, both $p<0.01$). Although GE was significantly accelerated between 150 and 330 min in T1DM receiving pramlintide, peak glucose levels did not exceed 138 ± 8 mg/dl in T1DM compared to PBO (178 ± 9 mg/dl, $p<0.01$). None of the volunteers reported nausea or bloating. **Discussion:** Gastric emptying was increased rather than delayed in T1DM and that may be an important contributor to PP hyperglycemia. The amylin analogue pramlintide delayed gastric emptying and significantly reduced PP hyperglycemia in T1DM. Modulation of gastric emptying is a promising tool in regulating intestinal nutrient flow and reducing PP glycemia

224355: Diabetes Induces Gender Dependent Changes in Gastric Neuronal Nitric Oxide Synthase (nNOS) Expression, Dimerization and Function. *Pandu R Gangula, Maria-Adelaide Micci, John Winston, Raj Kumar, Xiemin Cao, Pankaj J Pasricha*

Introduction: Both idiopathic and diabetic forms of gastroparesis, like many other disorders of gastrointestinal motility, predominantly affect women. However, the biological basis of this gender bias remains completely unknown. Based on the importance of neuronal nitric oxide synthase (nNOS) in the regulation of gastric motility, we explored the effect of gender on its expression and function in healthy and diabetic rats. **Methods:** Age-matched male and female Sprague-Dawley rats were used. Diabetic animals were studied 12 weeks after streptozotocin (55 mg/kg body weight, i.p.)-induced sustained hyperglycemia. Changes in gastric nNOS mRNA and protein levels were analyzed using real-time PCR and Western immunoblotting respectively. Both COOH- and NH₂-terminal nNOS antibodies were used to measure changes in expression of both total nNOS protein and the alpha homodimer in normal and diabetic gastric tissues. nNOS dimerization studies were performed using low-temperature SDS-PAGE. Nitrinergic relaxation (AUC/mg tissue weight) was studied after the application of electric field stimulation (EFS) to fundal, antral and pyloric tissues in an organ bath. **Results:** As compared with males controls (MC), gastric nNOS mRNA, protein expression and nitrinergic relaxation were significantly ($P<0.05$) elevated in healthy female control rats (FC) in all regions of the stomach. The active dimeric form and dimer: monomer ratio (DMR) of nNOS alpha were also higher in females compared to male rats ($P<0.05$). Interestingly, diabetic females (FD), but not males, showed significant ($P<0.05$) impairment in both nNOS alpha dimerization (Fundus FD 7.97 ± 0.02 vs. FC 22.31 ± 5.88 ; Antrum FD 15.6 ± 1.29 vs. FC 41.6 ± 3.02 ; Pylorus FD 3.4 ± 1.17 vs. FC 8.98 ± 0.82) and nitrinergic relaxation (Fundus FD -0.26 ± 0.06 vs. FC -0.55 ± 0.16 ; Antrum FD -0.07 ± 0.02 vs. FC -0.49 ± 0.19 ; Pylorus FD -0.22 ± 0.07 vs. FC -0.46 ± 0.09). **Conclusions:** This study demonstrates significant gender differences in gastric nitrinergic expression, and function in both health and disease. Nitrinergic relaxation is more pronounced in healthy females accounted, in part, by an increased expression of the active dimeric form of nNOS alpha. On the other hand, chronic hyperglycemia causes a greater reduction in active forms of nNOS in females associated with significantly more impairment of nitrinergic relaxation. This study also illustrates for the first time the importance of nNOS dimerization in gastric physiology. While we are still exploring the underlying mechanisms, these findings may provide a biological explanation for the greater vulnerability of females to develop diabetic gastroparesis.

224446: Neuropathological and Genomic Changes in the Stomach of Patients with Human Diabetic Gastroparesis. *harsha vittal, Gianrico Farrugia, Nonko D Pehlivanov, Matt S Lurken, Pankaj J Pasricha*

Background: The pathophysiological basis of diabetic gastroparesis is unknown, with almost no data on neuropathological and molecular changes in the stomachs of patients. The aim of this study is to use modern analytical methods to determine morphological and molecular changes in the gastric wall in patients with diabetic gastroparesis. **Methods:** Full thickness gastric biopsies were obtained laparoscopically from gastroparetic patients undergoing surgical intervention and from comparable disease-free areas of control subjects undergoing other forms of gastric surgery. Samples were processed for histological and immunohistochemical examination as well as mRNA preparation and gene expression analysis using Affymetrix Gene Chips. **Results:** As part of an ongoing study, specimens have been obtained from two patients with diabetic gastroparesis and two control subjects. Although both patients had severe refractory symptoms with malnutrition, requiring the placement of a gastric stimulator, one of them had no detectable abnormalities as compared with controls. This patient had an abrupt onset of symptoms with a short duration of well controlled diabetes and no significant episodes of ketoacidosis or hypoglycemia. By contrast, the other patient had long standing poorly controlled diabetes with numerous episodes of diabetic ketoacidosis and frequent hypoglycemic episodes. Histological examination in this patient revealed increased fibrosis in the muscle layers as well as significantly fewer nerve fibers and myenteric neurons as assessed by PGP9.5 staining. Further, significant reduction was seen in staining for nNOS, VIP and tyrosine hydroxylase as well as for c-KIT. By contrast, staining for substance P appeared to be increased. Analysis of mRNA expression confirmed some of these changes including a 1.9 fold decrease in Kit and 2.2 fold increase in tachykinin precursor 1 and indicated changes in several other potentially relevant genes such as a 1.5-fold reduction in tryptophan hydroxylase I, a 3.2-fold reduction in heme oxygenase 2 and a nearly 12-fold reduction in the muscarinic M3 receptor. **Conclusion:** Poor metabolic control in diabetes is associated with significant pathological changes in the gastric wall that affect all major components including muscle, neurons and ICC. However, severe symptoms can also occur in the absence of these changes and may reflect vagal, central or hormonal influences. Gastroparesis is therefore likely to be a

heterogenous disorder. Careful molecular and pathological analysis may allow more precise phenotypic differentiation and shed insight into the underlying mechanisms as well as identify novel therapeutic targets

222318: Predictive Factors for Clinical Improvement with Enterra Gastric Electric Stimulation Treatment for Refractory Gastroparesis. Jennifer L Maranki, Vanessa Lytes, John E Meilahn, Sean Harbison, Frank Friedenber, Robert S Fisher, Henry P Parkman

Gastric electrical stimulation (GES) treatment for refractory gastroparesis has been available for 5 years. Although studies have investigated the clinical effectiveness of this therapy, the clinical factors that predict a favorable response have not been addressed. The AIMS of this study were to: 1) to analyze the clinical response to GES in patients with refractory gastroparesis; and 2) to determine factors associated with a favorable response to Enterra GES treatment. METHODS: This clinical protocol was conducted prospectively at our institution in patients undergoing Enterra GES (Medtronic, Inc) for refractory gastroparesis under the FDA's Humanitarian Device Exemption program. Symptoms associated with gastroparesis were scored before and at regular intervals after GES implantation using the validated Gastroparesis Cardinal Symptom Index (GCSI) questionnaire with additional questions about abdominal pain and global clinical response. RESULTS: During an 18 month study period from 3/2004 to 9/2005, 29 patients (25 female, 4 male; mean age: 40 years) underwent implantation of Enterra GES. Follow-up data were available for 28 patients, with average follow-up of 148 days. At follow-up, 14 of 28 patients felt improved; 8 remained the same; and 6 worsened. The overall GCSI significantly decreased by $12\pm 7\%$ (SEM) (3.3 ± 0.2 to 2.7 ± 0.2 ; $p<0.05$) with improvement in the nausea/vomiting subscore ($30\pm 7\%$; $p<0.01$) and the postprandial subscore ($10\pm 10\%$; $p<0.05$), but no improvement in the bloating subscore or abdominal pain. The decrease in the GCSI was greater for the 12 diabetic patients ($18\pm 11\%$; $p<0.05$) than the 16 idiopathic patients ($7\pm 9\%$; $p=NS$). The subgroup of 22 patients with a chief complaint of nausea/vomiting had a greater improvement ($16\pm 9\%$; $p<0.05$) than the 6 patients with a chief complaint of abdominal pain ($3\pm 11\%$; $p=NS$). The 13 patients taking narcotic analgesics at the time of implant had a poorer response with the GCSI slightly increasing by $9\pm 10\%$ ($p=NS$) compared to the 15 patients who were not, whose GCSI scores decreased by $30\pm 8\%$ ($p<0.01$). There was no effect of gender, BMI, or hemoglobin A1c in diabetics on the clinical response. CONCLUSIONS: Gastric electric stimulation resulted in clinical improvement in 50% of patients with refractory gastroparesis. Three clinical parameters were identified to be associated with a favorable clinical response: 1) diabetic rather than idiopathic gastroparesis, 2) nausea/vomiting rather than abdominal pain as the primary symptom, and 3) independence from narcotic analgesics prior to stimulator implantation. Knowledge of these three factors may allow improved patient selection for gastric electric stimulation.

223947: A Sham-Controlled Study of Intra-Pyloric Injection of Botulinum Toxin In Gastroparesis. Joris Arts, Philippe Caenepeel, Lieselot Holvoet, Daniel Sifrim, Dominiek Dewulf, Verbeke Kristien, Jozef Janssens, Jan Tack

Recent uncontrolled studies in limited numbers of patients suggest a benefit of intrapyloric injection of botulinum toxin (botox) for the treatment of gastroparesis. Improvement seems to occur within the first 4 weeks, but controlled data are lacking. The aim of the present study was to investigate the effect of botox on symptoms and gastric emptying in gastroparesis in a double-blind randomised cross-over design. Methods: Consecutive gastroparesis patients underwent two upper gastrointestinal endoscopies with 4 weeks interval, during which intra-pyloric injection with saline or botox 4x25U was performed in a randomised double-blind fashion. Injections were prepared by a nurse who was otherwise not involved in the care of these patients. Before the start of the study and 4 weeks after each treatment, they underwent a solid and liquid 14C octanoic acid and 13C glycin gastric emptying breath test, and symptom severity was assessed using the Gastroparesis Cardinal Symptoms Index (GCSI). GCSI scores and gastric half emptying times ($t_{1/2}$) were calculated and results (mean \pm SEM), both parallel and pooled data, were compared using Student's t test. Results: 23 gastroparesis patients (5 men, mean age 45 ± 3 years, 21 idiopathic, 2 diabetic and 2 post-Nissen) were recruited; 12 received botox first and 11 saline first. After initial saline injection, significant improvement was seen for GCSI score and solid and liquid $t_{1/2}$ (respectively 32.1 ± 1.7 vs. 26.3 ± 2.2 ; 121 ± 14 vs. 87 ± 8 min and 107 ± 11 vs. 69 ± 6 min, all $p<0.01$). After the second injection, with botox, GCSI improved further to 21.4 ± 3.0 ($p<0.05$) while no significant changes were seen for solid and liquid $t_{1/2}$ (respectively 101 ± 17 and 81 ± 10 min, NS). Initial botox injection was associated with similar significant improvement of GCSI score and solid $t_{1/2}$ (respectively 21.3 ± 2.8 vs. 15.7 ± 3.2 , and 111 ± 7 vs. 93 ± 9 min, both $p<0.05$), while liquid $t_{1/2}$ did not reach significance (104 ± 30 vs. 76 ± 10 min, NS). No significant further improvement occurred after the second injection, with saline (GCSI 13.4 ± 3.3 , solid $t_{1/2}$ 94 ± 11 min and liquid $t_{1/2}$ 74 ± 8 min, all NS). When data for both treatment periods were pooled, no significant difference was seen for improvements respectively after botox or saline injection for GCSI (6.1 ± 1.5 vs. 3.8 ± 1.5 , NS), solid $t_{1/2}$ (3.4 ± 7.4 vs. 16.3 ± 8.3 , NS) and liquid $t_{1/2}$ (8.2 ± 13.7 vs. 22.5 ± 7.7 , NS). CONCLUSION: In a cohort of gastroparesis patients of predominantly idiopathic origin, intra-pyloric injection of botulinum toxin does not seem superior to placebo in improving symptoms and solid or liquid gastric emptying rate.

224572: Tegaserod Enhances Gastric Accommodation by Antagonizing 5-HT_{2b} Receptor Activity In the Gastric Myenteric Plexus And Smooth Muscle. *Ling Wang, Shi-Yi Zhou, Chung Owyang*

Tegaserod (T) is a potent 5-HT₄ receptor agonist with clinical efficacy in disorders associated with reduced GI motility and transit. T has been shown to enhance gastric accommodation in humans, but the underlying mechanism is unclear. In vitro studies indicate that T is not strictly selective for the 5-HT₄ receptor, as it has similar affinity for the 5-HT_{2B} receptor. We therefore investigated whether improved gastric accommodation evoked by T is mediated by 5-HT₄ or 5-HT_{2B} receptors. In vivo gastric accommodation studies were performed in anesthetized rats. A pressure transducer was inserted into the proximal stomach through the pylorus along with a catheter to infuse saline for gastric distension. Intra-gastric distension produced a stepwise increase in intra-gastric pressure (IGP). At 2 and 6 ml of gastric distension IGP increased 7.25±0.8 and 5.4±0.2 mmHg respectively. T (1mg/kg iv) significantly reduced this increase to 5.5±0.3 and 3.4±0.2 mmHg. T's action was dose dependent and not affected by a specific 5-HT₄ antagonist (SDZ-205,557, 1mg/kg). Similarly, vagotomy did not affect T's action, suggesting T acts directly on 5-HT receptors other than 5-HT₄ present in gastric myenteric plexus or smooth muscle. To investigate the effects of activation of 5-HT_{2B} receptors on gastric motility, we showed that administration of a 5-HT_{2B} agonist, α -methyl-5HT (0.03 mg/kg) increased IGP to 7.1±0.5 mmHg, which was dose dependently antagonized by T. Co-administration of SDZ-205,557 did not affect the antagonistic action of T suggesting T is a potent 5-HT_{2B} receptor antagonist. This action likely contributes to T's ability to enhance gastric compliance. High levels of both mRNA and protein for 5-HT_{2B} receptor were found in the gastric wall of rats by Rt-PCR and Western analysis. Immunocytochemistry showed 5-HT_{2B} receptors were present predominantly in the longitudinal and circular smooth muscle layers and myenteric plexus. To investigate the mechanisms by which activation of 5-HT_{2B} receptor increases gastric contractions, we showed that electrical field stimulation (1-20 Hz) of gastric muscle preparations resulted in a neuronally-mediated contractile response significantly potentiated by application of α -methyl-5HT (10-6M) (30% over control). Similarly α -methyl-5HT enhanced carbachol (10-9-10-6M) induced gastric contractions by 50%. This potentiation effect could be blocked by T (10-6M). Conclusion: T enhances gastric accommodation in rats. This action is not due to activation of 5-HT₄ receptors but appears to be related to 5-HT_{2B} receptor antagonist activity, which reduces the release of acetylcholine from the myenteric plexus and/or its actions on gastric muscle.

222095: Newer Antiepileptic Drugs for Adults with Cyclic Vomiting Syndrome (CVS): A Novel Approach to Maintenance Therapy. *Ray E Clouse, Gregory S Sayuk, Rajesh Shah, Patrick J Lustman, Chandra Prakash*

Management of CVS in adult patients is limited by the small number of effective agents either for abortive treatment of episodes or maintenance of the episode-free interval. Tricyclic antidepressants (TCAs) have been the most commonly used maintenance medications in adults, but their use often is limited by high side effect profiles. Newer antiepileptic drugs (AEDs), including zonisamide (Zonegran®, ZN) and levetiracetam (Keppra®, KP), are well tolerated, are being used for off-label prophylaxis against migraine headache, but have not been tested in CVS. Methods: 18 adult patients with CVS (mean age 38.6 ±3.3 yr; range 19-71; 7 female/11 male) were treated with maintenance open-label AEDs after TCA failure (13 pts) or intolerance (5 pts). Each patient had typical Rome II features of CVS; 9 (50%) also had a dominant abdominal pain component; and 5 subjects (28%) had a CVS picture in face of diabetes mellitus without other satisfactory explanation for the stereotypical vomiting episodes. 2 (22%) had personal or family history of migraine headache and 3 (9%) had prodromal features. 4 subjects had used marijuana regularly but had no improvement on withdrawal. Duration of CVS averaged 5.4 ±1.4 yr (range 0.2-21 yr), and episode rate over the 1 year pre-AED averaged 1.1 ±0.3/month. Each subject was followed for ≥3 months on AEDs; response to treatment was evaluated on a 0-3 Likert scale (worse/no improvement to near complete or complete response) with comparison to pre-treatment course. Results: 15 subjects (83%) were treated with ZN and 3 (17%) with KP; median final daily dose (range) was 300 mg (100-600 mg) for ZN and 1000 mg (500-2000 mg) for KP. TCAs were discontinued in 10 subjects (75%). Duration of follow-up on AEDs averaged 9.7 ±2.0 mo. Response ≥2 on the Likert scale (at least moderate response) occurred in 13 (72%) of subjects, while complete or near complete resolution of episodes was reported by 8 of these (44% of total). Episode rate reduced to 0.5 ±0.2/mo (p<0.05 compared with pre-AED value) for responders. Only 1 subject was intolerant (CNS side effects from ZN). Conclusions: Newer AEDs, specifically ZN and KP, are beneficial in open-label, maintenance use for reducing vomiting episodes in adults with CVS. Nearly three-fourths of subjects who were unsatisfactorily managed with TCAs benefited over this short follow-up period. Further investigation of these AEDs in CVS is indicated to better define efficacy, dosing and drug superiority. Considering their high tolerance and lower side effect profiles, they may prove superior to TCAs in primary maintenance strategies.

222711: A Dose-Ranging, Double-Blind, Placebo-Controlled Study of Lubiprostone in Subjects with Irritable Bowel Syndrome and Constipation (c-IBS). *John F Johanson, Raymond Panas, P. Christopher Holland, Ryuji Ueno*

IBS is a condition that affects nearly 30 million individuals in North America and accounts for 25-50% of the referrals to gastroenterologists. Lubiprostone is a novel type-2 chloride channel (ClC-2) activator that has been shown to be efficacious and well tolerated in a number of well-controlled clinical trials in subjects with chronic constipation. We present the results from a

12-week dose-ranging study where lubiprostone was tested, for the first time, exclusively in subjects with IBS with constipation (c-IBS), as defined by the Rome II Criteria. **Methods:** Approximately 50 subjects were randomized in a double-blind fashion to each of the four treatment groups: placebo (0 µg) or 16, 32, or 48 µg lubiprostone daily (8, 16, or 24 µg BID). In an electronic diary, subjects recorded data relating to dosing, abdominal symptoms (bloating and discomfort/pain), bowel movements (BMs; frequency and straining and consistency ratings), and rescue medication use. Weekly diary questions queried subjects on their assessment of the treatment effectiveness. Trend-tests were used to detect dose-dependent efficacy relationships and a step-down testing procedure was used to make pairwise comparisons between the active lubiprostone and placebo groups in the case of a dose-dependent trend. Safety was assessed by adverse event (AE) incidence rates. **Results:** Significant dose-dependent trends were observed during at least 2 of the 3 months for abdominal discomfort/pain, abdominal bloating, spontaneous BM frequency (SBM), stool consistency, bowel straining, and assessments of constipation severity. Pairwise comparisons revealed many significant differences between the active groups and placebo. During months 1 and 2, improvements in abdominal discomfort/pain and SBM frequency rates were more than doubled in all lubiprostone groups as compared to placebo. Specifically, at Month 1, decreases from baseline in abdominal discomfort (based on a 5-point scale) were 0.19, 0.45, 0.40, and 0.46 points in the placebo, 16, 32, and 48 µg groups, respectively; at Month 2, decreases from baseline were 0.23, 0.52, 0.53, and 0.54 points, respectively; and, at Month 3, decreases from baseline were 0.34, 0.56, 0.59, and 0.53 points, respectively. Overall, improvements were typically highest in the 48 µg group. With respect to safety, dose-dependent trends were also observed. AE incidence and drop-out rates typically increased with increasing dose. **Conclusion:** Lubiprostone is an efficacious and well-tolerated treatment for c-IBS. Dose-dependent trends were observed with respect to safety and efficacy.

Additional Reading: Motility Disorders: Top to Bottom

219398: Reduced Pain Perception in Barrett's Esophagus (BE) Patients is likely due to Downregulation of TRPV1 Receptors in the Squamous Epithelium Rather than in the Barrett's Mucosa Itself. *Ram Dickman, Pankaj J Pasricha, John Winston, Mohan Shenoy, Diley Hernandez, Harinder S Garewal, Ronnie Fass*

Background: Patients with BE demonstrate reduced pain perception. It is currently assumed that this is due to the presence of columnar, metaplastic epithelium that is less sensitive to acid. **Aims:** To compare the distal esophageal expression of TRPV1, a receptor that is gated by protons and is suspected to mediate heartburn sensation, in the squamous and columnar metaplastic epithelium of BE patients to erosive esophagitis (EE) patients and normal controls. **Methods:** Five normal, healthy controls, 5 patients with EE and 5 with BE were recruited into the study. All participants underwent an upper endoscopy to ascertain their diagnosis. BE was defined as any columnar-like extension into the tubular esophagus that is positive on biopsy for intestinal metaplasia. In all groups, 2 biopsies were obtained from normal appearing mucosa in the distal esophagus, 6 cm > esophagogastric junction. Two additional biopsies were taken from the Barrett's tissue in BE patients. TRPV1 expression was analyzed by Western blots. **Results:** The mean age and M/F ratio was, 49.8 ± 8.9 yrs, 3/2 for healthy controls, 52.0 ± 3.5, 3/2 for EE and 62 ± 4.3, 5/0 for BE, respectively. The mean length of the Barrett's mucosa was 5.9 ± 0.5 cm (4.5-7.0 cm). The distribution of erosive esophagitis grading as Grade A - 1, Grade B - 3 and Grade C - 1. Patients with BE had the lowest expression of TRPV1 receptors in the squamous epithelium (0.3771) as compared with EE (0.4167) and healthy controls (0.5151) (p < 0.05). In contrast, the TRPV1 receptors expression within the Barrett's tissue was the highest (0.9652) when compared to the TRPV1 expression in the squamous epithelium of all other groups (p < 0.05). **Conclusions:** Patients with BE have the lowest TRPV1 receptors expression in the distal esophageal squamous epithelium, but at the same time the highest TRPV1 receptors expression within the Barrett's tissue when compared to EE patients and healthy controls. It is likely that the observed reduction in pain perception of BE patients is due to downregulation of TRPV1 within the esophageal squamous epithelium and not within the Barrett's mucosa.

216298: Sensory and Biomechanical Properties of The Esophagus after Nissen Fundoplication. *Jose M Remes-Troche, Ranjit Mudipalli, James Maher, Satish SC Rao*

Introduction/Aim: Previously, we have shown that prolonged acid reflux can induce significant sensory-motor changes in the esophageal wall in patients with GERD (Am J Gastroenterol 2001; 96(1):S24). Whether these changes are reversible with definitive therapy for GERD is not known. Our aim was to prospectively assess sensory and biomechanical properties of the esophagus before and after Nissen Fundoplication (NF). **Methods:** Graded balloon distensions were performed using impedance planimetry to assess sensory and biomechanical properties of the esophageal wall in 6 patients with refractory symptoms and with endoscopic + 24-hr pH study evidence of GERD (M/F= 3/3, mean age=43 years), and in 12 matched healthy volunteers (M/F= 6/6, mean age=43 years). GERD patients underwent a baseline evaluation and a repeat evaluation, at least 12 months after surgery (range 13-44 months). Sensory thresholds were evaluated using a 4 point Likert scale. Data were analyzed with ANOVA and paired t test. **Results:** Before NF, the cross sectional area (CSA) of the esophageal wall was higher (p<0.05*, Table) and the circumferential wall tension/strain relationship was decreased in patients with GERD compared to healthy controls. After NF, when compared to baseline, CSA and esophageal wall reactivity decreased (p<0.05) and the wall tension/strain relationship increased. The biomechanical parameters after NF were similar to healthy controls. Before NF,

sensory thresholds were lower in GERD patients compared to controls; first perception (mean ± SE, cm H₂O; 13±2 vs 30±3, p<0.01), discomfort (34±4 vs 54±4, p<0.01) and pain (49±7 vs 62±2, p<0.01). After NF, there were no changes in these thresholds (first perception =13±3, discomfort =37±7, and pain =53±6, p= NS) **Conclusions:** The esophagus has a larger lumen and the esophageal wall is stiffer and less deformable and is hypersensitive in patients with GERD. After NF, the biomechanical abnormalities improved but sensory thresholds were unchanged. Thus, antireflux surgery appears to correct the esophageal biomechanical dysfunction(s) in patients with GERD, but not the underlying hypersensitivity. This finding may explain persistent symptoms in some patients, after Nissen fundoplication.

Changes in biomechanical properties in GERD patients and controls

Balloon pressure →	10 cm H ₂ O			40 cm H ₂ O		
	Before	After	Control	Before	After	Control
CSA (mm ²)	310±56*	191±27	119±30	734±99*	551±70	469±18
Reactivity (mm ²)	84±16*	56±10	43±4	232±63*	123±84	199±28
Strain	.35±.1*	.41±.1	.40±.01	1.04±.1*	1.36±.2	1.34±.1

mean±SD *p<0.05 vs after and controls

226561: Continuous Pyloric Manometry Determines the Effectiveness of Botulinum Toxin Injection in Patients with Gastroparesis. *Linda Anh B Nguyen, Shelly Parker, Stephen Bunker, William J Snape*

Background: Gastroparesis is a disorder of gastric motility that results in delayed gastric emptying in the absence of mechanical obstruction. Pylorospasm (tonic pyloric contractions ≥10mmHg) has been implicated in gastroparesis(Mearin et al.Gastro 1986). Botulinum toxin A injection (80-200 U) into the pylorus has been shown in a number of studies to improve symptoms and gastric emptying. The success rate has been variable. Gupta and Rao(Gastrointest Endosc 2002) showed that botulinum toxin(BT) attenuated isolated pyloric pressure waves on ambulatory antropyloroduoenal manometry 3 weeks after injection with 200 units of BT. Our hypothesis is that the subset of patients with pylorospasm are the patients who would benefit from BT injection. Aims:1)Evaluate the feasibility of recording pyloric pressures using a Dent sleeve before and immediately after the injection of BT and 2)Correlate post-injection pyloric pressures with clinical response. Patients and Methods: 7 patients with gastroparesis (4 diabetics, M=6, age 35.1±2.5, mean 4hr gastric retention 23.5%±6.9) underwent upper endoscopy with pyloric pressure measurements using a Dent sleeve (Mui Scientific). Positioning of the sleeve was confirmed fluoroscopically. Basal and peak pyloric pressures were measured before and immediately after BT injection. The Dent sleeve was left in position during BT injection. Patients with tonically elevated basal pyloric pressures received a total of 100 units of BT injection into the pylorus. 3 patients had a follow up gastric scintigraphy (1,3 and 18 days) after the injections. One patient underwent 2 treatment sessions after not responding to the first injection. Results: Basal pyloric pressures (PP) and peak PP decreased immediately after the injection of BT (28.8 mmHg±5.2 vs. 9.9 mmHg±2.1, p=0.002; 68.5±8.3 vs. 34.8±5.4, p=0.01). 3 patients who were hospitalized had immediate improvement and were discharged from the hospital 2 days later. The 3 patients who improved, had their basal PP decrease from 12.8 to 0, 33.0 to 7.0 and 14.7 to 7.6mmHg, respectively. Two patients who did not have symptomatic improvement had post BT basal PP the decreased but remained elevated at 18.7 and 17.0. The patient whose basal PP decreased from 38.6 to 18.7 had an improvement in gastric emptying but not symptoms. This patient had a second procedure 3 weeks later where the post BT pressure decreased to 10.9, at which point he symptomatic improvement. Conclusions: 1)Pyloric pressures decrease immediately following BT injection. 2)Since 100 units of BT did not reduce basal PP to <10 mmHg in all patients, this may indentify patients who need higher doses of BT.

226913: Role of Pyloric Pressures and Botulinum toxin (BT) injection in the Treatment of Diabetic (DM) and Idiopathic Gastroparesis (IG). *Katerina Shetler, Linda Anh B Nguyen, Stephen Bunker, Shelly Parker, William J Snape*

Background: Pylorospasm (basal pyloric pressures >10mmHg; Mearin et al. Gastro 1986) has been implicated in gastroparesis. BT injection into the pylorus has been suggested to reduce symptoms and improve gastric emptying in patients with gastroparesis. It is unclear whether pyloric pressures correlate with gastric emptying. Aims: 1)Correlate baseline pyloric pressures with gastric scintigraphy(GET) in patients with DM and IG. 2)Determine the effect of BT injection on GET in patients with DM and IG. Patients and Methods: 35 patients [(19 DM, age 41.3±10.3 years) and (16 IG, age 48.8±13.1)] had pyloric manometry and GET. 17 of these patients were treated with BT injection into the pylorus and had follow up GET. Delayed gastric emptying was defined as gastric retention > 60% at 2 hours or > 10% at 4 hours. Pyloric manometry was done during upper endoscopy by marking the pylorus with a hemoclip. A Dent Sleeve was placed across the pylorus using fluoroscopic guidance. The amplitude of the tonic and phasic contractions were measured using the intragastric pressure as a zero point. 100 U of BT was injected into the pyloric sphincter in patients with elevated pyloric pressures. Results: The 4hr GET was higher for DM (49.9±21.0 %) than for IG (33.9±24.6%), p <0.05. The mean basal pyloric pressure was similar in patients with DM (15.4±13.5 mmHg) and IG (13.8±7.7 mmHg). Baseline pyloric pressures were elevated above a normal

pressure of >10 mmHg in 11(57.9%) patients with DM and in 10(62.5%) patients with IG. Correlation between baseline pyloric pressure and 4 hour GET was assessed using a linear regression analysis. The baseline pyloric pressure correlated poorly with 4 hour GET in both groups (DM: $r=-0.012$, $p=0.48$ and IG: $r= 0.07$, $p=0.4$). Of the patients who received BT, there was no difference in basal pyloric pressures (DM= 20.4 ± 5.1 mmHg vs. IG= 13.8 ± 2.6 mmHg, $p=0.26$) Repeat GET was done after a mean follow up period of 31.4 ± 7.2 days (range: 2-120 d). GET did not change after BT injection in the DM group(4hr: $66.8\pm 8.4\%$ to $76.8\pm 11.5\%$, $p= 0.48$ and 2hr: $44.6\pm 7.6\%$ to $53.6\pm 12.2\%$, $p=0.054$). There was a trend toward improved GET in the IG group but it was not statistically significant ($60.3\pm 6.1\%$ to $50.5\pm 7.8\%$ at 2 hours, $p=0.34$; $27.8\pm 5.9\%$ to $14.3\pm 7.7\%$ at 4 hours, $p=0.18$). Conclusions: 1)Pylorospasm is present in approximately 60% of patients with gastroparesis. 2)There is no correlation between basal pyloric pressures and gastric emptying. This suggests that other factors affect gastric emptying, especially in the DM group. It would be important to correlate antral activity, pyloric pressures and GET, especially in those patients who do not respond to BT.

222607: Gastroduodenal Motility Measured in Health and Disease During Transit of an Ambulatory Capsule-SmartPill. *Mihaela Podovei, Marek Majewski, Annabel N Yuen, Braden Kuo, Irene Sarosiek, John Kuhn, Laura Negron, Jack R Semler, Connor Semler, Richard W McCallum*

Introduction: Differences in GI luminal pressure patterns between healthy normals (N) and patients with gastroparesis (GP) could give insight into pathophysiology. Pressure measurements in the antrum and duodenum have traditionally been performed with invasive indwelling manometry catheters. SmartPill is a wireless ambulatory capsule that measures luminal pH and pressure as it courses throughout the GI tract after being swallowed. Passage of the indigestible solid SmartPill from the stomach into the duodenum appears to occur near the end or soon after the gastric emptying of a solid meal or during the fasting state when MMCs occur. Aims: To compare pressure patterns between normal subjects and patients with gastroparesis as defined by a previously abnormal gastric scintigraphy. Methods: In 2 centers, healthy subjects and patients swallowed the SmartPill (SP) after an overnight fast together with a standardized meal of 120 g Eggbeaters, 2 pieces of bread with jam; 255 kcal, 2% fat) and 120 cc water. The rapid pH change from acidic to alkaline (>3 unit rise from baseline gastric pH) marked the emptying of the ingested SmartPill from the stomach into the duodenum. The frequency and amplitude of contractions recorded by the capsule were counted in 30 minute intervals from 60 min before gastric emptying (GE) to 60 min after the capsule left the stomach. These parameters for Ns and GPs were then compared for each time interval by two-sample unequal variance T test. Results: 21 Ns (13M/8F, mean age 30.8) and 16 GPs (4M/12F, mean age 40.9 (9 diabetic/7 idiopathic)) were studied. Mean contraction frequency and pressure amplitudes in both groups for 30 min intervals are summarized in the table below. Gastroparetics had lower gastric contraction frequencies in the time period -60 to -30 min (preceding gastric emptying) compared to normals, $p<0.02$. There were no differences in contraction amplitudes between the 2 groups. Conclusion: 1. This new ambulatory technology represented by SmartPill detected impaired gastric (antral) motility in GP compared to normals. 2. Decreases in frequency in gastroparetics prior to emptying of an indigestible solid may reflect neurogenic abnormalities in Phase II fasting response. 3. Contraction patterns in health and disease throughout the gut can be measured with the SmartPill Capsule.

	30-60 m before GE	0-30 m before GE	0-30 m after GE	30-60 m after GE
N Freq (#contr/min)	1.2	1.3	2.0	2.0
GP Freq(#contr/min)	0.7	1.3	1.7	1.7
P val	0.01	0.93	0.46	0.44
N Ampl(mmHg)	26.7	39.1	21.5	16.6
GP Ampl(mmHg)	29.0	49.6	25.4	17.7
P val	0.74	0.36	0.08	0.42

218303: Gastroscopy Guided Implantation of Temporary Gastric Electrodes: A New Minimal Invasive Technique. *Hasse R Abrahamsson, Anders Elfvin, Stina Andersson, Anders Edebo, Magnus Simren, Hans Lonroth*

Temporary (temp) leads have been used for gastric electrical stimulation (GES) to evaluate whether gastroparetic patients (GP pts) respond to GES (Abell et al 2002&2005). Previous techniques required general anesthesia, or an oral or PEG route. We have elaborated a simple, minimal invasive principle for electrode implantation and tested the appropriateness of placement in animals and in pts by various recording and stimulation techniques. METHODS: Leads were constructed so that the tip of the lead could be anchored to the gastric submucosa. Part I: Acute 1-2 hr experiments (expts) were performed in anesthetized pigs. Under endoscopic control two leads were introduced and gastric EMG (G-EMG) recorded. Part II: Three pts (1 male, M; 2 females, F) with drug refractory nausea (N) and/or vomiting (V) with non-established indications for GES were evaluated with percutaneous temp leads, implanted at gastroscopy (slight sedation plus local skin anesthesia). Detailed studies of electrode

function were done measuring distance between electrodes (fluoroscopy), impedance, G-EMG compared with manometry and the effect of temp GES for 7-9 days on symptoms (sympt) (stimulator: Enterra, Medtronic, 12 imp/min, 5mA). Diagnoses and main sympt were: chronic intestinal pseudoobstruction (CIP; 1 F, V+N), functional dyspepsia (FD) without GP (1 F, N; 1 M, V). RESULTS: Part I: In the pigs a slow wave (SW) rhythm, 3-4/min, was recorded throughout the expts with some decrease in frequency at the end of expt. SWs were accompanied by a second potential, suggestive of phasic contractions. Part II: In the pts implantation time from start of gastroscopy to end of electrode placement was 12-20 min. Electrode distance varied from 12 to 45 mm. Impedance was 1100-420 ohm at gastroscopy, decreased after implant in 2 pts and was 510-629 on day 7-9. G-EMG showed a regular SW rhythm about 3/min. Antral pressure waves had intervals being multiples of the SW to SW-time observed in each patient. With temporary GES for 7-9 days weekly frequency of main sympt decreased: CIP, F: N 20 to 1 hrs, V 7 to 1. FD, F: N 17 to 1hrs; M: V 5 to 3/w. The sympt decrease was independent of electrode distance. No complications from the leads or lead extraction were noted. Permanent implant and 1 yr follow up showed very good results in the two pts with marked effect of temp GES (CIP; FD, F), the third pt (FD, M) had moderate effect at 1 yr. CONCLUSIONS: Temporary percutaneous gastric leads can easily be implanted at endoscopy and may be used for testing of GES and study of gastric electrophysiology.

225348: Diabetic Gastroparesis : Effect of Mitemincin by Subgroup Analysis in a 12-week, Randomized, Multi-center, Double-blind, Placebo-controlled, Phase 2b Study. *Richard W McCallum, Barry J Goldstein*

INTRODUCTION: Mitemincin, a macrolide derived motilin-receptor agonist can accelerate gastric emptying (GE) time in patients with idiopathic and diabetic gastroparesis. Obesity and poor glycemic control are thought to be independent risk factors for upper GI symptoms. We investigated how these factors affected placebo response and examined Mitemincin efficacy in the subgroup using an eligibility baseline cut-off of BMI<35kg/m² and/or HbA1c<10%. METHODS: 392 insulin-requiring pts with type 1 or 2 DM were stratified by gastric emptying test results (solid meal scintigraphy, per site standard) and treated for 3 months with placebo (P), Mitemincin 5mg or 10 mg BID. Complete Response (CR) required positive monthly response (defined at least twice of “adequate symptom relief” in weekly global assessments of a month) for all 3 months. Overall Response (OR) required at least 75% of the weekly global assessments to be positive for the whole treatment period. 145 of 392 pts were excluded for: lack of baseline data (36 total: 9 BMI, 23 HbA1c, 4 both), BMI>=35 (89), HbA1c>=10% (18), both factors (7). Study subset (247 patients) included: 74% type 1: 26% type 2; 62% female: 38% male; and 52% delayed: 48% non-delayed. RESULTS: Multivariate analysis in P demonstrated significant influences on placebo response rate by BMI (Odds Ratio 3.08, 95% CI 1.00-9.46) and gender (2.73, 1.02-7.29). DM type, GE status, age and HbA1c affected PR rate without achieving statistical significance; DM history and symptom severity were not predictive. Multivariate analysis in ITT identified BMI<35 subgroup for CR of Mitemincin 10 mg vs. P (2.29 OR; 1.09-4.82, 95%CI). The Weekly Response, CR and OR rates (%) for pts with baseline HbA1c<10% and BMI<35 are reported. CONCLUSIONS: 1) A significantly higher response rate was seen in mitemincin treated patients; 2) BMI and gender were independent covariates for a greater placebo response; 3) Insulin requiring diabetics with symptomatic gastroparesis who have a BMI<35 and HbA1c<10% may represent a subset of study patients more likely to accurately reflect a clinically meaningful response with mitemincin at 10 mg bid; 4) Tachyphylaxis to Mitemincin was not observed over the 3-month double-blind study period. 5) Additional trials with mitemincin in diabetic gastroparesis and other gastropathies are warranted. [Research funded by Chugai Pharma USA, LLC]

BMI<35 + HbA1c<10% (n=247)	Mean Weekly Response Rate (%)			CR rate (%)			OR rate (%)		
	P (n=82)	5 mg (n=94)	10 mg (n=68)	P (n=82)	5 mg (n=95)	10 mg (n=70)	P (n=82)	5 mg (n=95)	10 mg (n=70)
	28.4 ± 29.4	34.9 ± 31.6 (0.158)	44.8 ± 34.8 (0.002)*	15.9	24.2 (0.168)	34.3 (0.008)*	9.8	17.9 (0.121)	32.9 (0.0004)*

Mean ± SD (P value)

222021: A 10-Day Course of Rifaximin, A Non-Absorbable Antibiotic, Produces A Durable Improvement In All Symptoms of Irritable Bowel Syndrome: A Double-Blind Randomized Controlled Study. *Mark Pimentel, Sandy Park, Yuthana Kong, Kimberly Low, Soumya Chatterjee, Hyo-rang Lee*

Recent data suggest a relationship between gut bacteria and IBS symptoms such that improvement in IBS is observed after antibiotic treatment. We have recently reported the beneficial effects of rifaximin, a non-absorbed antibiotic, on global improvement in IBS. In this sub-analysis, the component symptoms of IBS and their response to rifaximin are determined. Methods: Rome I criteria positive IBS patients were enrolled in a double-blind randomized placebo-controlled study. After a 1-week run in, subjects were asked to complete a symptom questionnaire with diarrhea, constipation, bloating and abdominal pain rated on a VAS score from 0-100mm after which a lactulose breath test was conducted. Subjects were then randomized to rifaximin 400mg or placebo tid for 10-days. One week after completion of treatment, subjects repeated their questions. Thereafter, for an additional 9 weeks, subjects completed a weekly symptom questionnaire. The number of subjects with > 50% improvement in each of the symptom categories was determined over the 10-week follow-up time period. Two endpoints were examined. The first endpoint was one week after completing treatment. The second was the overall 10-week period. Results: 87

subjects were randomized in the study (44 placebo, 43 rifaximin). One week after rifaximin, 48.6% of subjects demonstrated a clinical response with diarrhea (>50% improved) compared to 23.5% for placebo ($p<0.05$). For bloating, 34.9% of subjects demonstrated relief compared to 18.6% for placebo ($p=0.07$). At this first endpoint, constipation and abdominal pain were not improved. When the proportion of patients with clinical improvement (>50% improvement) was determined for the entire 10-week follow-up period for each symptom, all four symptoms were statistically improved including bloating (49.2 ± 6.8 vs. $22.6\pm 3.5\%$, $p<0.0000001$), diarrhea (50.6 ± 5.7 vs $35.3\pm 6.3\%$, $p<0.00001$), abdominal pain (39.7 ± 7.4 vs $28.9\pm 7.2\%$, $p<0.01$) and constipation (35.1 ± 7.0 vs $28.1\pm 5.0\%$, $p<0.05$). Conclusions: Rifaximin treatment results in a significant improvement in the four major symptoms of IBS for 10 weeks after completion of treatment.