W1040

Optimal Treatment Duration of Glyceryl Trinitrate (GTN) for Chronic Anal Fissure (CAF): Results of a Prospective Randomized Multicenter Trial

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Background: Optimal treatment duration of GTN for CAF is unknown. Methods: Prospective randomized trial comparing 40 vs. 80 days with twice daily topical 0.4% GTN treatment (Rectogesic®, Prostrakan Group) for CAF. Chronicity was defined as presence of fibrosis or skin tag or visible sphincter fibers or hypertrophied anal papilla and symptoms present for more than 2 months or with pain of less duration but similar episodes in the past. A chronicity score (the sum of anatomical chronic features) and a validated gravity score were used. Fissure healing, the primary aim of the study and maximum pain at defecation measured with VAS were assessed at baseline (which included manometry) and at 2, 4, 6, 8 weeks and at 80 days, when data was gathered. Results: Of 188 patients with chronic fissure 96 were randomized to the 40 days treatment and 92 to the 80 days treatment. Patients were well matched for sex, age, presence of chronic features, fissure scores. There were 35 (19%) patients (21 in the 40 days group and 14 in the 80 days group) who did not complete treatment 14 (40%) because of side effects 5 (11%) because of worsening symptoms, 3 (9%) for both and 13 (37%) did not attend scheduled visits. Of 151 patients who completed the assigned treatment 79 (52%) had their fissures healed and 92 (61%) were pain free. There was no difference in healing and absence of symptoms between the two groups. At the analysis of variance there was a significant improvement in the paired VAS scores between baseline, 2 weeks, 4 weeks and 6 weeks ($p<0.001$) while there was no additional improvement between 6 weeks and 80 days. Average VAS scores were lower among patients assigned to 80 days ($p<0.01$). Final pain score was not different between groups ($P=0.33$). Persistence of pain was associated with presence of fibrosis ($p<0.05$), advanced age ($p<0.05$), high maximum resting pressure ($p<0.005$), high fissure gravity score ($p=0.005$) and longer duration of symptoms ($p<0.01$). Failure to heal was correlated with higher chronicity score ($p<0.05$) and visible sphincter fibers ($p<0.05$). Conclusion: Pain at defecation from CAF continues to improve up to 6 weeks of topical GTN treatment and is on average lower in patients treated longer then 40 days. Fissures with more chronic features are less likely to heal even after 80 days of treatment.

W1041

SP-304 to Treat GI Disorders - Effects of a Single, Oral-Dose of SP-304 On Safety, Tolerability, Pharmacokinetics and Pharmacodynamics in Healthy Volunteers

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Purpose: SP-304 is a new member of a novel class of non-systemic drugs for treatment of chronic constipation (CC), irritable bowel syndrome with constipation (IBS-C) and other GI diseases. SP-304 is a synthetic analog of uroguanylin, a natriuretic hormone that regulates ion and fluid transport in the GI tract. Orally administered SP-304 binds to and activates guanylate cyclase C (GC-C) expressed on the epithelial cells lining the GI mucosa, resulting in activation of the cystic fibrosis transmembrane conductance regulator (CFTR), and leading to an augmented flow of chloride and water into the lumen of the gut to facilitate bowel movement. In animal models, oral administration of SP-304 promotes intestinal secretion and ameliorates gastrointestinal inflammation. The purpose of this first clinical study with SP-304 was to characterize the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) effects of the drug in healthy volunteers. Methods: A double-blind, placebo-controlled, randomized single, oral, ascending dose (0.1 mg to 48.6 mg) study was performed in 71 healthy male and female volunteers. Subjects were evaluated for safety, tolerability, PK and PD effects of SP-304. Adverse events (AE) were evaluated using Common Terminology Criteria for Adverse Events (CTCAE), version 3. Pharmacodynamic effects were evaluated by the time to first stool and by the 7-point Bristol Stool Form Scale (BSFS) to monitor stool consistency. Results: SP-304 was well-tolerated at all dose levels with no unexpected side effects reported. No SAEs were observed at all dose levels throughout this study. No measurable systemic absorption of orally administered SP-304 occurred at all dose levels studied ranging from 0.1 mg to 48.6 mg (validated SP-304 serum assay sensitive down to 10 ng/ml). Although this trial was not powered for statistical significance, SP-304 appeared to decrease the time to first bowel movement and elicited an increase in the post-dose BSFS versus placebo. Conclusions: In this single-dose Phase I study in volunteers, SP-304 was well-tolerated across all doses (0.1 mg to 48.6 mg) and exhibited pharmacodynamic activity in healthy volunteers with no detectable systemic absorption. We intend to pursue further clinical development of SP-304 to treat patients with CC and IBS-C.

W1042

Mechanistic Population Pharmacokinetics (PK) Model of PF-00547659, a Fully Human IgG2 Anti-MAdCAM Antibody, in Ulcerative Colitis Patients: Results of a First in Human (Fih) Study

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INTRODUCTION: MAdCAM (mucosal adressin cell adhesion molecule) is expressed on high endothelial venules of intestinal lymphoid tissue and expression is increased at sites of GI inflammation. MAdCAM binds a4b7 integrin on lymphocytes facilitating their migration to the inflamed intestinal tract. PF-00547659 is a fully human IgG2 anti-MAdCAM antibody which by blocking MAdCAM/a4b7 dependent lymphocyte recruitment to the gut is anticipated to reduce gut inflammation and mucosal damage. METHODS: This double-blind placebo-controlled FIH study was designed to test efficacy, safety and PK endpoints. Thirty patients were included in 6 single-dose cohorts (0.03 to 10 mg/kg IV, 3.0 mg/kg SC or placebo) and an additional fifty in 5 multiple-dose cohorts (0.1 to 3.0 mg/kg IV and 0.3 to 1 mg/kg SC or placebo). The PK characteristics of PF-00547659 were determined through nonlinear mixed-effect modelling (NONMEM, version VI). RESULTS: The PK of PF-00547659 was best described by a 2-compartment disposition model incorporating first-order absorption following SC dosing. Following SC doses 0.3 to 3.0 mg/kg, Cmax was observed on day 7 in the majority of subjects. Elimination was best described by 2 parallel pathways: A linear, non-specific pathway typical of monoclonal antibodies (half-life ~28 days) and a specific pathway represented by PF-00547659 binding to MAdCAM with subsequent internalization and elimination of the complex (termed target mediated disposition, TMD). TMD was fully saturated at doses ≥1mg/kg. Incorporation of MAdCAM into the model allowed estimation of the turnover rate and degree of suppression of MAdCAM. The volume of distribution (~5 L) indicated that the antibody remained predominately within the vasculature which is ideal since MAdCAM is located on high endothelial venules. The model predicted that MAdCAM levels were completely suppressed for 10 to 12 weeks in the majority of subjects following single doses of 3 to 10 mg/kg. No anti-drug antibodies were detected. CONCLUSION: The pharmacokinetics of PF-00547659 was typical of a monoclonal antibody with sustained concentrations at high doses. TMD was observed at low doses due to MAdCAM binding and clearance. PF-00547659 remained primarily within the vasculature near its target site. Following a single dose of 3 or 10 mg/kg, serum levels were maintained for up to 3 months with model-predicted complete suppression of free MAdCAM for the same duration in the majority of subjects and in the absence of any anti-drug antibodies being detected.

W1043

GI Consultations in Pregnancy

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Background: Training in gastroenterology requires understanding gastrointestinal (GI) disorders in pregnancy. While broad understanding is ideal, determining which conditions are most commonly referred for consultation may be helpful in focusing trainee education and preparing for future practice. However, this has not been done. The purpose of this study was to review the GI consultations at a high-volume obstetrics hospital to determine the reasons for consultation in pregnancy and the final diagnoses. Methods: A chart review of all consecutive outpatient consultations for pregnant women at Women & Infants' Hospital between October 1, 2004 and October 17, 2007 was performed. 370 charts were reviewed. Referring source, patient characteristics, reason for consultation, diagnosis (based on ICD-9 code), change in management after consultation and need for follow-up were recorded. Established patients who became pregnant during the study period were excluded. Results: 75.6% of women requiring GI consultation in pregnancy were referred by Ob/Gyn. Primigravidas comprised 36.7% of patients. The mean weeks gestation at the time of consultation was 21.3 + 8.8. 35.4% of consultations were for new GI symptoms arising in pregnancy, 24.4% for worsening of a pre-existing GI disorder, 15.1% for GI symptoms recurring in a subsequent pregnancy and 3.0% for medication safety recommendations. The most common reasons for consultation were viral hepatitis (20.2%), nausea and vomiting (18.9%) and abdominal pain (13.5%). 30.5% of patients were diagnosed with a liver disorder in pregnancy (viral hepatitis 11.6%, chronic non-viral hepatitis 5.5%, abnormal LFTs 5.4%, liver disorder unique to pregnancy-e.g. cholestasis of pregnancy, HELLP syndrome-3.8%, other 4.2%). The most frequent non-hepatologic diagnoses were hyperemesis gravidarum (20.8%), GERD (16.2%) and constipation (13.0%). As a result of consultation, 84.5% of patients underwent diagnostic testing. Consultation led to a change in diagnosis in 25.1% of cases and to a change in management in 78.6%. 77.3% of patients required GI follow-up during pregnancy and 37.8% required follow-up post-partum. Conclusions: Viral hepatitis, nausea and vomiting and abdominal pain are the most common reasons for GI consultation in pregnancy. One-third of patients were diagnosed with a liver disorder. The most common non-hepatologic diagnoses were hyperemesis gravidarum, GERD and constipation. GI consultation changed patient management in the majority of cases. Gastroenterologists should be familiar with the evaluation and management of these conditions in pregnancy as they are most likely to be the reasons for consultation.

W1044

Introducing GI Wiki: An Online Point-of-Care Resource for Gastroenterology Fellows, Faculty and Clinicians

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The Gastroenterology Core Curriculum represents the collective wisdom of multiple gastroenterology (GI) societies regarding the scope of gastroenterology training. While the curriculum outlines the knowledge and skills expected to be acquired during fellowship training, it does not provide the actual content per se. The main aim of GI Wiki is to provide a comprehensive, continuously updated point-of-care reference for GI trainees and faculty based on the Gastroenterology Core Curriculum. The GI Wiki (http://giwiki.org) is built on a web-based wiki platform that allows users to create, edit, and link web pages easily. This allows fellows to assimilate and share their learning as they are being exposed to various clinical cases and seminars during their fellowship. Content authors (GI trainees and faculty) are required to log-in and verify their credentials before given privileges to add or modify content. The wiki editorial board tracks revisions and has ability to correct or roll back to a previous version. The GI Wiki consists of chapters outlined according to the core curriculum, and links to resources: online pharmacopoeia, recommended reading list, guidelines; and GI-specific online calculators (see Figure). By restricting authoring and editing access to GI trainees and practitioners, our hope is to develop a high-quality, peer-authored, reliable resource as a ready reference for fellowship training programs. As the user-community of GI Wiki expands, and with it new content gets created or edited, we plan to formally evaluate the relevance and accuracy of content in GI Wiki. The beta version of the GI Wiki (available online at http://giwiki.org) went live on July 2008 and currently has 15 complete chapters and links to online resources. Audience will get a chance to interact with GI Wiki and add/edit content from a networked workstation at the meeting.