intestinal permeability can be supposed. More studies are needed to explain the pathogenetic involvement of the intestinal barrier at each level, in SNAS condition.

Sa1373

Abnormal Histology in Patients With Diarrhoea and Normal Colonoscopy:- Incidence and Clinical Correlates

Martyn Dibb, Salil Singh, Rejy Joseph, David Shelton, Stephen Hayes, Peter Paine

INTRODUCTION/OBJECTIVES: In patients with chronic diarrhoea, random colon biopsies are routinely taken in macroscopically normal colons to exclude microscopic colitis. Its reported incidence varies from 1 - 10/100,000 with higher incidence in the elderly and in females.[1] Histological changes which do not fulfill specific diagnostic criteria for microscopic colitis are regularly found. The incidence and relevance of such abnormalities are unknown. Our aim was to investigate the incidence and clinical correlates of colonic histological abnormalities in patients with chronic diarrhoea and a normal colonoscopy. **AIMS & METHODS:** All colonoscopy examinations at a UK teaching hospital from 2006 - 2008 with diarrhoea as part of the procedure indication were included. Exclusion criteria were a history of colitis and macroscopic abnormalities accounting for diarrhoea. Age, gender and presenting symptoms were collected. In addition, presenting symptoms were extracted from clinical records. A gastrointestinal pathologist second reported all abnormal histology. **RESULTS:** 842 patients fulfilled the inclusion criteria (mean age 51, range 17-92, 62% female). Abnormal histology was identified in 234 (28%). Collagenous colitis was found in 2% (61, 25-83, 71% female) and lymphocytic colitis in 1% (60, 23-85, 60% female) (Table 1). Compared to those with normal histology, these patients were older ($p<0.04$) but no specific symptom/gender pattern was associated. Non-specific inflammatory changes that did not fulfil microscopic colitis criteria were found in 17% (49, 17-87, 58% female). Once again, no specific symptom/age/gender pattern was found. **CONCLUSION:** Our study finds an incidence of microscopic colitis of approx 10/100,000. Inflammatory histological changes that did not fulfill any alternative diagnostic criteria were found in 1 in 6 patients. Presenting symptoms in this group did not differ from those with normal histology. Bowel cleansing agents have been occasionally attributed as the cause of such findings despite a lack of supporting evidence. Whilst the long-term outcome in these patients is unknown, it is important to establish that presenting symptoms are not correlated with these histological abnormalities. **REFERENCES:** 1. Williams JJ; Kaplan GG; Makhija S et al. Microscopic colitis-defining incidence rates and risk factors: A population-based study. Clin Gastroenterol Hepatol. 2008 Jan;6(1):35-4

Table 1. Colonic histology in patients with chronic diarrhoea and normal colonoscopy.

Histology	N=842	Percentage (%)
Normal	608	72.2
Collagenous colitis (diagnostic/borderline)	13/4	1.5/0.5
Lymphocytic colitis (diagnostic/borderline)	9/1	1.1/0.1
Minimal change	19	2.3
Melanosis coli	17	2.0
Drug change	17	2.0
Microscopic colitis not otherwise specified	141	16.7
Inflammatory bowel disease	13	1.5

Sa1375

The Combination of Indomethacin and Bile Acid is Directly Damaging to Intestinal Cells and Can Be Made Less Toxic by Complex Formation With Phosphatidylcholine

Elizabeth Dial, Lenard M. Lichtenberger

Background: Indomethacin (Indo) is a potent anti-inflammatory and analgesic drug, but is limited in use due its side effect of GI bleeding. To explain this adverse effect, we have proposed that Indo can form toxic mixed micelles with bile acid (deoxycholate) which may directly injure gastric and intestinal cells (Am J Physiol 298:G722-31, 2010). Additionally, the chemical association of phosphatidylcholine (PC) with Indo (2:1 by weight) may render mixed bile acid micelles less injurious (Br J Pharmacol 157:252-7, 2009). Methods: To further test this hypothesis with an expanded number of bile acids, an *In Vitro* system using rat intestinal cells (IEC-6) was established. IEC-6 cells were incubated for 3 h with non-injurious concentrations of Indo (2.5 mM), Indo-PC, bile acid (deoxycholate, 0.3 mM; cholate, 4 mM; chenodexoycholate, 0.6 mM; their tauro- and glyco-conjugates), or combinations of Indo/Indo-PC and bile acid. Injury was assessed by cytosolic lactate dehydrogenase (LDH) release into the media and by viable cell number. Cellular uptake of bile acid (taurocholate) and Indo was monitored with radioisotopes at 6 and 37°C, in sodium or choline buffers, and with potential receptor blocking agents. Results: LDH was increased and cell number decreased, indicating injury, when Indo was combined with any of the bile acids, including the conjugates. In contrast, Indo-PC was not damaging in the presence of the same bile acids and conjugates. There was no evidence for active uptake of either the bile acid or Indo into the IEC-6 cells, and the passive uptake of bile acid or Indo was not affected by the other agent. The use of receptor blocking agents (lactic acid or benzoic acid for Indo; 25-hydroxycholesterol for bile acid) did not consistently affect damage from the combination of bile acid and Indo. Conclusions: At appropriate concentrations, Indo and most bile acids can form a complex that is directly toxic to intestinal cells. The initial injury from bile acid/Indo appears to be at the cell membrane rather than intracellular. The pre-association of PC with Indo reverses the toxicity of Indo alone and directly protects intestinal cells. Indo-PC offers a potential therapeutic benefit through reduced GI injury. (Supported by NIH grant RC1DK086304).

Sa1376

Pharmacological Characterization of FE 203799, a Novel Long Acting Peptide Analog of Glucagon-Like Peptide-2 (GLP-2)

Diane M. Hargrove, Sudar Alagarsamy, Steve Qi, Karthik Srinivasan, Glenn Croston, Regent Laporte, Javier Sueiras-Diaz, Kazimierz Wisniewski, Jennifer Hartwig, Halina T. Wisniewska, Mark Lu, Alexander P. Posch, Claudio D. Schteingart, Pierre J. Rivière

GLP-2 is a 33 amino acid peptide that is released from intestinal L-cells following nutrient ingestion and acts at distinct G protein coupled GLP-2 receptors in the small intestine and colon to potently stimulate intestinal growth. GLP-2 also increases nutrient absorption, stimulates mesenteric blood flow and modulates gastrointestinal motility. GLP-2 agonists are efficacious in animal models of disease including models of large and small bowel inflammation, short bowel syndrome and chemotherapy- and radiation-induced mucositis suggesting they may have therapeutic potential for the treatment of gastrointestinal diseases and disorders. Clinical development of GLP-2 agonists is testing this hypothesis. Peptides are widely believed to have rapid clearance and a short half-life, limiting their clinical utility. Indeed, native GLP-2 has a short circulating half-life due to cleavage by dipeptidyl peptidase IV (DPP4) limiting its development as a therapeutic agent. A DPP4 resistant analog of GLP-2 (teduglutide, h[Gly2]GLP-2 (1-33)) with somewhat lower clearance than GLP-2 is in clinical trials in patients with short bowel syndrome. Herein we report on the characterization of FE 203799, a novel GLP-2 analog that retains potency and selectivity at the hGLP-2 receptor and has a greatly improved pharmacokinetic (PK) and pharmacodynamic profile. *In Vitro* potency (EC_{50}) at the hGLP-2 receptor was determined using HEK-293 cells transiently co-transfected with hGLP-2 receptor and a cAMP responsive luciferase reporter plasmid. The EC_{50} values for hGLP-2, FE 203799 and teduglutide were 0.07, 0.03 and 0.09 nM respectively. In rat PK studies, FE 203799 was shown to have dramatically lower clearance than GLP-2 or teduglutide, resulting in a long half-life. Following intravenous (IV) bolus administration, the elimination half-life of FE 203799 was 8- and 25-fold longer than teduglutide and hGLP-2 respectively. The half-life of FE 203799 was even longer following subcutaneous (SC) administration. Treatment with FE 203799 resulted in greater *In Vivo* potency to achieve pharmacodynamic efficacy for stimulation of intestinal growth in rats, likely stemming from the observed increase in half-life. These unique properties of FE 203799 relative to analogs currently in clinical trials may confer a superior therapeutic profile for the treatment of gastrointestinal diseases.

Pharmacokinetic (PK) and pharmacodynamic profiles

	FE 203799	teduglutide	hGLP-2
Rat PK			
Elimination half-life (minutes), IV	159	18.7	6.4
Terminal half-life (minutes), SC	701	30.9	^
SC bioavailability (F_{SC}%)	74	63	^
Intestine weight in rats*			
Dosing interval: 24 hours, 30 nmol/kg, SC	37.0%	15.3%	^
Dosing interval: 48 hours, 30 nmol/kg, SC	23.4%	7.6%	^

*Small intestine wet weight over vehicle treated; intestines collected 96 hours after first dose. ^Not tested

Sa1377

Identification of New Genetic Biomarkers Predicting the Blood Concentration of Azathioprine Administrated With 5-Aminosalicylic Acid as Combination Therapy for Inflammatory Bowel Disease

Kazuhiko Uchiyama, Yuji Naito, Tomohisa Takagi, Norihiko Kondo, Yasunori Iwamoto, Shumpei Ishikawa, Naohisa Yoshida, Osamu Handa, Takeshi Ishikawa, Hiroaki Yasuda, Junichi Sakagami, Hideyuki Konishi, Naoki Wakabayashi, Nobuaki Yagi, Satoshi Kokura, Toshikazu Yoshikawa

BACKGROUND AND AIMS Thiopurines are widely used for the treatment of patients suffering from malignancies, rheumatic disease, or inflammatory bowel disease (IBD). The dose of thioprine often has to be reduced, or the therapy has to be discontinued in 9 - 28% of patients because of adverse drug reactions (ADRs). Azathioprine (AZA), used as immmunosuppressant for the treatment of IBD, is catabolized by thioprine methyltransferase (TPMT), which exhibits genetic polymorphisms. It has also been reported that 5-aminosalicylic acid (5-ASA) inhibits TPMT activity, and that increased 6-thioguanine nucleotide (6-TGNs) concentration results in an increased number of ADRs. Though polymorphisms of TPMT have been reported to be related to ADRs by AZA, the mechanism of ADRs induced by AZA has not been completely understood yet, especially in combination with 5-ASA. In this study we attempted to identify single nucleotide polymorphisms (SNPs) related to differential gene expression, influencing the AZA drug metabolism in combination therapy with 5-ASA. Such SNPs may be used as markers for the prediction of individual AZA blood concentration. METHODS To identify genetic biomarkers for the prediction of 6-TGN blood concentration, 30 different immortalized HapMap lymphocyte cultures (Japanese individuals) were used. We carried out an ExpressGenotypingTM analysis which is able to detect critical pharmacogenetic SNPs by analyzing the differences in allelic gene expression in cell cultures. This method is based on genome-wide SNP expression analysis on Affymetrix microarrays and detects drug-induced expression allelic imbalance (EAI). The lymphocyte cell cultures were treated with AZA and 5-ASA in combination, and drug-induced EAI plus linked SNPs were analyzed. We further tried to corroborate the resulting candidate SNPs in clinical samples from patients treated with combination therapy of the both drugs. For analysis of the gene expression profile the lymphocyte cell cultures were treated with 10 mM AZA. For marker candidate verification blood samples from 30 IBD patients were used. RESULTS We detected more than 100 probes with an EAI value of ≥2 within the 30 investigated cell cultures. The respective genes were analyzed in the IBD patients' blood samples. Among these probes we found anti-inflammatory genes, drug-metabolizing enzymes, ABC transporter