T1318

Incidence of Small Bowel Injury By Low-Dose Enteric-Coated Aspirin, and Efficacy of Misoprostol in Treating It - A Pilot Study with Capsule Endoscopy

Toshio Watanabe, Satoshi Sugimori, Natsuhiko Kameda, Hirotoshi Okazaki, Tetsuya Tanigawa, Kenji Watanabe, Kazunari Tominaga, Yasuhiro Fujiwara, Nobuhide Oshitani, Kazuhide Higuchi, Tetsuo Arakawa

Background: Although nonsteroidal anti-inflammatory drugs have recently been reported to frequently cause small bowel injury, no effective treatment for this type of injury has been established. Although use of low-dose enteric-coated aspirin is associated with decreased risk of gastroduodenal ulceration, the ulcerogenic effect of aspirin on the small intestine remain unclear. Aims: To determine the incidence of small bowel injury in chronic users of low-dose enteric-coated aspirin and the efficacy of misoprostol in treating this type of injury by capsule endoscopy. Methods: 9 patients (6 males and 3 females, median age 65 years, age range 57-75) found to have gastric ulcers on endoscopy during treatment with low-dose enteric-coated aspirin for primary or secondary prevention of cardiovascular disease were enrolled in this study. They continued aspirin therapy, but added proton pump inhibitors (PPIs, omeprazole 20 mg/day or rabeprazole 10 mg/day) for 8 weeks to heal gastric ulcers. They then received misoprostol 200 micrograms qid instead of PPIs for 8 weeks. Capsule endoscopy was performed after 8-week PPI treatment, and repeated after 8-week misoprostol therapy. Results: All patients underwent first capsule endoscopy, while three individuals subsequently withdrew before completing the study protocol (2 developed severe watery diarrhea and 1 discontinued aspirin during misoprostol treatment). First capsule endoscopy revealed red spots and mucosal breaks (erosions/ulcers) in 100% (9/9) and 89.9% (8/9) of patients, respectively. The median numbers of red spots and mucosal breaks were 5 (range, 2-52) and 3 (range, 0-32), respectively. In most patients, small intestinal lesions were found in both jejunum and ileum. In 6 patients who completed the study protocol, misoprostol significantly decreased the median numbers of red spots from 16.5 (range, 3-52) to 3.5 (range, 2-46, p=0.014) and the median numbers of mucosal breaks from 4.5 (range, 2-32) to 0.5 (range, 0-6, p=0.046). Conclusions: These findings suggest that low-dose enteric-coated aspirin may frequently damage the small intestine, and that misoprostol may be effective in treatment of aspirin-induced small intestinal injury.

T1319

Significance of Antibiotic Resistant *Helicobacter pylori* in a Chinese Population of Asia

Kwong Ming Fock, Dhamodaran Subbiah, Eng Kiong Teo, Tiing Leong Ang, Jessica Tan, Kieron B. Lim, David Ong

Introduction: There is significant geographical variation in the resistance patterns of *H. pylori* (Hp). Consistent data with strict monitoring on clarithromycin and metronidazole resistance is lacking in Asian countries. Metronidazole and Clarithromycin are widely used in Hp eradication. The European Hp Study Group recommends the use of clarithromycin & amoxicillin or metronidazole as the first-line therapy. Treatment failure is not uncommon and is often associated with resistant Hp strains. As eradication therapy is commenced empirically, local resistance rates of Hp isolates will have a significant clinical impact. We studied the resistance of metronidazole and clarithromycin among patients with endoscopically proved non ulcer dyspepsia (NUD) and duodenal ulcers (DU) from 2002 - 2006 in our centre. Aim: To determine the prevalence of Hp resistance to metronidazole and clarithromycin in patients with NUD & duodenal ulcers in our centre. Materials & Methods: Hp isolates were grown from gastric mucosal biopsy specimens obtained from 130 Chinese patients (75 males and 55 females) with NUD & DU was included in this study. Hp isolates were subcultured and E-tests were performed on agar plates with 5-7% added sheep blood. The antibiotic breakpoints employed for the E-test were >8 mg/L for metronidazole and >1 mg/L for clarithromycin. Results: Of the 130 Hp strains analysed, metronidazole resistance was observed among 51 (39%) and clarithromycin resistance among 12 (9%) strains. Hp strains were isolated from patients with age group 26-79 yr. with the average of 46 yr. We observed more metronidazole resistance among NUD group compared to DU group ($p<0.001$). Resistance of metronidazole and clarithromycin was not found to be associated with age and sex factors ($p>0.05$). Resistance to both antibiotics was observed among 3 (2.3%) Hp isolates from NUD group. Conclusion: This rise in the antibiotic resistance calls for the need to closely monitor local Hp resistance patterns. More research is needed to monitor the resistance of Hp to amoxycillin and tetracycline, as these drugs are administered with increasing frequency in Hp eradication. Quadruple therapies containing both clarithromycin and metronidazole were the most efficacious; over 80% of Hp infections were consistently eradicated with these regimens. Our data shows that local resistance rates of metronidazole and clarithromycin are similar to the currently available international data. Drug resistance is a strong predictor of efficacy across triple therapies for the eradication of Hp in adults.

T1320

The Herbal Extract, Iberogast, Partially Improves Small Intestinal Integrity in Rats with Mucositis Induced By 5-Fluorouracil

Tessa H. Wright, Ross N. Butler, Kerry A. Lymn, Roger Yazbeck, Ker Y. Cheah, Eleanor J. Whitford, Guy R. Sander, Gordon S. Howarth

Background: Currently there is a deficiency in effective treatments for mucositis, a severe side-effect of cancer chemotherapy. Iberogast (STW 5) is a naturally-occurring plant extract reported to possess anti-oxidant and anti-inflammatory properties. The current study investigated the potential for Iberogast to reduce the severity of 5-Fluorouracil (5-FU)-induced small intestinal damage in rats. **Methods:** Mucositis was induced in rats by administration of 5-FU on day 9. Rats were gavaged daily with Iberogast (0.1mL/mL) from day 3 (after acclimatisation) to day 11. Treatment groups (n=8), saline+water, 5-FU+water and 5-FU+Iberogast were then compared. Metabolism parameters including bodyweight, food and water intake and urine and faecal output, were measured daily. 13C-sucrose breath tests were performed on days 3, 9 and 12 to assess total sucrase activity non-invasively. At sacrifice, on day 12, small intestinal tissues were measured, weighed and collected for qualitative and quantitative histological analysis, and sucrase and myeloperoxidase (MPO) assay. Statistical analysis was by one-way ANOVA. **Results:** Significant increases in villus height (23%; 277±9μm), crypt depth (40%: 67±3μm) and mucosal thickness (26%: 172±27μm) were evident in 5-FU+Iberogast-treated rats compared to 5-FU+water-treated controls (48±2μm, 224±13μm and 136±24μm, respectively) ($p<0.05$). Moreover, overall histological disease severity (ODS) was decreased by 30% in 5-FU+Iberogast-treated rats (median score = 15.7) compared to 5-FU+water-treated rats (median score = 22.6). Jejunum+Ileum weight (g) was decreased in 5-FU+water (2.24±0.05) and 5-FU+Iberogast (2.20±0.05)-treated rats, compared to saline+water (2.54±0.05) controls ($p<0.05$). Significant reductions ($p<0.05$) in sucrase activity were observed in 5-FU+water and 5-FU+Iberogast-treated rats compared to saline+water controls. **Conclusions:** Iberogast partially-reduced histopathological features of mucositis, improved villus integrity and crypt structure, and increased mucosal thickness in the proximal jejunum of chemotherapy-treated rats. These promising findings warrant further investigation into the potential application of Iberogast in mucositis, and the mechanisms by which it exerts its beneficial effects.

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An Extract from Grape Seed Protects IEC-6 Cells from Chemotherapy-Induced Cytotoxicity and Improves Parameters of Small Intestinal Mucositis in Rats with Experimentally-Induced Mucositis

Ker Y. Cheah, Susan E. Bastian, Ross N. Butler, Caroline Payne, Kerry A. Lymn, Roger Yazbeck, Tessa H. Wright, Eleanor J. Whitford, Guy R. Sander, Gordon S. Howarth

Background: Grape seed extract (GSE) represents a rich source of procyanidins with the potential to exert anti-oxidant and anti-inflammatory activities within the gastrointestinal tract. We investigated GSE for its capacity to decrease the severity of chemotherapy-drug-induced mucositis *In Vitro* and *In Vivo*. **Methods:** The phenolic content and antioxidant levels of GSE were determined by Folin-Ciocalteu assay and Ferric Reducing Antioxidant Power (FRAP) assay, respectively. GSE was administered to IEC-6 intestinal epithelial cells with damage induced by methotrexate (MTX) or 5-fluorouracil (5-FU) and cell viability was determined by methylene blue assay. Rats were gavaged with GSE daily (400mg/kg) from day 3 (after acclimatization) to day 11. 5-FU (150mg/kg) was administered on day 9 to induce mucositis. Rats were sacrificed at day 12 and intestinal tissues collected for myeloperoxidase (MPO) assay, sucrase activity assay and qualitative and quantitative histology. Statistical analysis was performed by one-way ANOVA. **Results:** GSE comprised 43% phenolic content and attained a FRAP value of 1.2mg/mL compared to ascorbic acid control (3mg/mL). GSE (5 and 15 μg/mL) prevented the decrease in IEC-6 cell viability induced by MTX (0.3 μM/mL) ($p<0.05$). GSE significantly reduced MPO activity (U/g) by 86% (75±51) and 27% (82±5), respectively in the proximal jejunum ($p<0.001$) and distal ileum ($p<0.05$) compared to 5-FU controls (530±46 and 114±8). GSE significantly decreased the overall qualitative histological scoring ($p<0.05$; median score=24) compared to 5-FU treated controls (median score=29). GSE increased villus height in the proximal jejunum (17%; $p<0.05$; 277±8μm) and distal ileum (50%) ($p<0.01$; 217±14μm) compared to 5-FU treated controls (238±9μm and 144±8μm) and significantly attenuated the 5-FU-induced (287±8μm and 186±10μm) reduction of mucosal thickness by 16% (334±7μm) and 45% (270±18μm), respectively in the jejunum ($p<0.05$) and ileum ($p<0.01$). **Conclusions:** GSE protected IEC-6 cells from MTX-induced cytotoxicity and partially-ameliorated intestinal damage induced by 5-FU in rats. GSE may represent a promising new prophylactic adjunct to conventional chemotherapy treatment for intestinal mucositis. Moreover, the indications of GSE bioavailability in the distal intestine suggest further therapeutic potential for inflammatory disorders affecting the large bowel.

T1322

Safety and Tolerability of Prucalopride (Resolor®) in Patients with Chronic Constipation: Pooled Data from Three Pivotal Phase III Studies

Jan F. Tack, Jannie Ausma, Rene Kerstens, Lieve Vandeplassche

Objective: Prucalopride (PRU) is a selective high affinity 5-HT_4 agonist. Studies have shown that PRU effectively improved bowel movements in patients with chronic constipation (CC). In the current analysis, the safety and tolerability of PRU in a large dataset of CC patients was investigated. **Methods:** Three pivotal phase III double-blind, randomized, placebo (PLA)-controlled studies were conducted, identical in design. Trials consisted of a 2 week baseline period followed by a 12 week treatment period in which patients were randomized to once daily treatment with PRU 2 mg, PRU 4 mg or PLA. Adverse events (AEs) were reported and vital signs, laboratory and ECG were recorded at baseline, weeks 4 and 12 of treatment. Data from the 3 trials were pooled. **Results:** Eighty-nine percent of a total of 1924 ITT subjects were female, average age was 47 years, average history of constipation was 20 years and patients reported an average of only 0.5 spontaneous complete bowel movements per week. PRU 2 mg, PRU 4 mg and PLA were administered to 659, 657 and 661 patients, respectively. AE incidence is summarized in the table below. The higher incidence of headache, nausea and diarrhea in the PRU groups can be explained by the pharmacodynamic effect of PRU. Most AEs (≥5%) considered at least moderate in severity and possibly related to PRU were mainly related to the GI tract with a higher incidence in the PRU groups for nausea, diarrhea, abdominal pain and headache ranging from 2.7% to 4.7% in PLA *vs.* 5.1% to 11.8% in PRU 2 mg and 6.1% to 16.1% in PRU 4 mg. No deaths were reported. The only SAE reported in ≥1 patient was abdominoplasty for 2 patients in the PRU 4 mg group (not related to study medication). Most frequent AEs (≥2%) leading to discontinuation were nausea, diarrhea, abdominal pain and headache (varying from 0.2% to 0.9% for PLA, 0.9% to 1.8% for PRU 2 mg and 2.3% to 3.7% for PRU 4 mg). No clinically relevant differences were observed between PRU and PLA in laboratory parameters, in vital signs or ECG values during the trial period. **Conclusions:** Treatment during 12 weeks with prucalopride 2 mg and 4 mg is safe and well tolerated by patients with chronic constipation.