G0932

ASTHMA AND GASTROESOPHAGEAL REFLUX: THE INFLUENCE OF BRONCHODILATOR THERAPY ON REFLUX-ASSOCIATED DYSPNEA. G.H. Micklefield, I. Greving, D. Schött, B. May, University Hospital Bergmannsheil, Bochum, Germany

The association between asthma and gastroesophageal reflux disease has been extensively investigated recently. Almost all bronchodilators have relaxing effects on esophageal smooth muscle. The rate ofgastroesophageal reflux and reflux-associated dyspnea may be increased in some patients with asthma. The aim of this study was to evaluate, if therapy with fenoterol, ipratropiumbromide and theophylline induces reflux-associated dyspnea (symptoms correlated with esophageal pH) in patients with asthma.
Three groups were investigated: theophylline (30 patients), fenoterol (33 patients), ipratropiumbromide (27 patients). Esophageal manometry and 24-hour esophageal pH testing were performed with and without the drugs.
Theophylline reduced the resting pressure of the lower esophageal sphincter from 13 ± 4 to 7 ± 2 mm Hg ($p < 0.001$). No significant changes were seen for fenoterol and ipratropiumbromide. Theophylline increased reflux time from 7 ± 4 to 13 ± 5% ($p < 0.005$). No significant changes were seen for fenoterol and ipratropiumbromide.
Reflux-associated dyspnea: In 4 patients without theophylline, in 17 patients with theophylline ($p < 0.03$); in 5 patients without fenoterol, in 6 patients with fenoterol (NS); in 3 patients without ipratropiumbromide, in 3 patients with ipratropiumbromide (NS).
Inhalative fenoterol and ipratropiumbromide do not provoke reflux-associated dyspnea. The prevalence of reflux-associated dyspnea in patients with asthma during therapy with oral theophylline is significantly increased. Therefore, therapy with theophylline should be performed cautiously.

G0933

ESOPHAGEAL MANOMETRY IN PATIENTS WITH STROKE WITH AND WITHOUT DYSPHAGIA. G.H. Micklefield, E. Jørgensen, I. Blaeser, J. Jörg, J. Köbberling, Departments of Internal Medicine and Neurology, Klinikum Wuppertal GmbH, Wuppertal Germany

Review of the literature reveals practically no data regarding esophageal dysfunction resulting from stroke. Attention has been focused on the pharynx as the source of disability when neurological disease is associated with dysphagia. The aim of this study was to avaluate, if patients with stroke and oropharyngeal dysphagia also have a pathological esophageal motility.
In 19 stroke patients without oropharyngeal dysphagia and in 17 patients with oropharyngeal dysphagieal conventional multilumen esophageal manometry was performed. Esophageal motility was recorded within two days after admittance to our clinic.
No significant differences were found as to the following esophageal motility parameters: resting pressure of the lower esophageal sphincter, resting pressure of the upper esophageal sphincter, contraction amplitude, contraction velocity. Primary contractions in the tubular esophageal showed significant differences between the two groups. Distal esophagus: 93.5 ± 1.1% in patients without oropharyngeal dysphagia, 53.5 ± 5.4% in patients with oropharyngeal dysphagia ($p < 0.0001$). Proximal esophagus: 93.2 ± 3.4% vs. 62.1 ± 7,3% ($p < 0.0001$).
The reduced amount of primary contractions in the tubular esophagus is possibly responsible for the observed symptoms in some patients with stroke and oropharyngeal dysphagia.

● G0934

MECHANISMS OF ASPIRIN-MEDIATED PGHS-2 GENE INDUCTION IN A HUMAN INTESTINAL SUPEPITHELIAL MYOFIBROBLAST CELL LINE. R.C. Mifflin, J.I. Saada, J.F. DiMari, J.D. Valentich, and D.W. Powell. Department of Internal Medicine, The University of Texas Medical Branch, Galveston, TX.

Intestinal subepithelial myofibroblasts (ISEMF) are important mucosal targets and sources of proinflammatory cytokines and lipid mediators. We have previously shown that IL-1 induces prostaglandin H synthase-2 (PGHS-2) expression in the human ISEMF-derived cell line 18Co. We also observed that aspirin (1.0 to 5.0 mM) induces PGHS-2 expression and when combined with IL-1 leads to synergistic induction of PHGS-2 mRNA and protein. The present study was undertaken to determine the mechanisms of aspirin-mediated PGHS-2 induction and if other nonsteroidal antiinflammatory drugs (NSAIDS) have a similar effect.
Methods: **1.)** Confluent 18Co cultures were incubated 24 hours in the presence of NSAIDS (ibuprofen, piroxicam, indomethacin, 6-MNA, NS-398, 5-ASA, acetaminophen, Na-salicylate) to assay for their ability to induce PGHS-2 mRNA and protein using Northern analysis and Western analysis, respectively. **2.)** Confluent 18Co cultures were subjected to nuclear run-on analysis following aspirin treatment to determine whether the aspirinmediated induction occurs transcriptionally or post-transcriptionally. **3.)** Metabolic inhibitors (PDTC, SB-203580, N-acetylcysteine, genistein, herbimycin), were also employed to elucidate signal transduction pathways utilized by IL-1 or aspirin. **4.)** The lipoxygenase inhibitor NDGA (10-100 μM) was used to determine whether lipoxygenase products play a role in the aspirin-mediated induction. **5.)** c-Jun N-terminal and P38 kinase activities were assayed following IL-1 or aspirin treatment. **6.)** RT-PCR and Northern analysis of total RNA isolated from IL-1, aspirin, and IL-1 plus aspirin-treated cells was employed to determine if expression of other genes involved in growth and inflammation was affected by aspirin treatment.
Results: **1.)** Ibuprofen, Na-salicylate, and NS-398 were capable of inducing PGHS-2 expression at levels similar to those seen following aspirin treatment, **2.)** There was a very close correlation between the PGHS-2 transcriptional activity in the nuclear run on assays and the observed level of protein and mRNA induction, **3.)** Inhibitor studies indicate that IL-1 and aspirin act through similar pathways which involve tyrosine phosphorylation, activation of P38 mitogen activated protein kinase, and generation of reactive oxygen intermediates to induce PGHS-2 expression, **4.)** NDGA (100μM) had no effect upon IL-1 or aspirin mediated PGHS-2 induction, **5.)** Increased P38 and c-Jun N-terminal kinase activities were detected within 30 minutes of IL-1 treatment but not following aspirin treatment, and **6.)** Aspirin treatment resulted in increased mRNA levels for IL-6, ICAM, hepatocyte growth factor, and heme oxygenase-I.
Conclusions: Aspirin and other NSAIDS enhance expression of PGHS-2 and other genes active in growth and inflammation at the level of transcription via mechanisms that involve tyrosine phosphorylation and possible activation of stress or mitogen-activated protein kinases. These data raise interesting questions about mechanisms of NSAID-induced GI damage unrelated to inhibition of PGHS activity. (Supported by NIH Grant DK15350).

G0935

THE AMAZONIAN HERBAL REMEDY, SANGRE DE GRADO (DRAGON'S BLOOD), HEALS EXPERIMENTAL GASTRIC ULCERS IN PART VIA AN ANTIBACTERIAL ACTION. M.J.S. Miller, H. Sadowska-Krowicka, C. Tinoco, M. Sandoval. Department of Pediatrics, Louisiana State University Medical Center, New Orleans, LA.

A number of herbal treatments leading to new therapeutic approaches to disease have originated from the Amazon river basin. In this study we set out to evaluate the sap of *Croton draconoides*, which is a traditional medicine amongst indigenous people for wound healing and the treatment of gastrointestinal distress and viral and microbial infections. Gastric ulcers were induced in anesthetized rats by brief serosal application of acetic acid. Rats were allowed to recover and either received no further treatment or diluted Sangre de Grado (1:1000 to 1:10,000 fold) in the drinking water. After 7 or 14 days the rats were anesthetized and euthanized, ulcer size was determined by image analysis (histologically and from gross appearance) along with myeloperoxidase (MPO) activity and bacterial content of the ulcer. In untreated rats, serosal application of acetic acid resulted in a large craterous, inflamed ulcer that was colonized by gramnegative bacteria (mainly *E.coli*). Treatment with Sangre de Grado resulted in a dramatic reduction in the bacterial content of the ulcers from 6.9×10^9 to 3.6×10^7 at the lowest does ($p < 0.01$). Ulcer MPO activity was reduced from 647 ± 124 to 165 ± 20 Units and ulcer size was also reduced by approximately 20% at all doses. Continuation of therapy to 14 days further reduced gastric bacterial load and promoted ulcer healing. This effective therapy is a potentially cost effective treatment of gastrointestinal distress in impoverished communities. A 14-day treatment protocol with Sangre de Grado costs approximately 25 cents, well below the costs for standard antibiotic therapy.

● G0936

EFFECTS OF INTERLEUKIN-8 ON HISTAMINE RELEASE FROM RAT ECL CELLS. Y Minagawa, H Tomono, K Yakabi, T Nakamura. The Third Department of Internal Medicine, Teikyo University School of Medicine (Ichihara hospital), Chiba, Japan

Background: Interleukin-8 (IL-8) which is a major chemotactic peptide for neutriphil is increased in the gastric mucosa with Helicobacter pylori (H. pylori) infection. IL-8 was assumed to be partially resposible for the inflammation of gastric mucosa. On the other hand, the abnormality of gastric acid secretion was also shown in H. pylori infection. Several cytokines are supposed to be involved in the abnormality of gastric acid secretion in H. pylori infection. There might be great possibilities that cytokines would influence the functions of ECL cells which is a major histamine secreting cells in the mechanism of acid secretion. In this study, we undertook to elucidate effects of IL-8 on histamine release from ECL cells which had important roles in the stimulation of parietal cells through histamine release.
Methods: A combination of elutriation and Nycodents density gradient centrifugation was used to purify rat fundic ECL cells. Enrichment was determined by the immunostaining with anti histamine antibody, toluidine blue staining, and electron microscopy. Enriched ECL cells were incubated in the medium with gastrin, carbachol, concanavalin A and IL-8 for 60min. at 37°C. Contents of histamine in the incubation medium were assayed by histamine RIA kit (IMMUNO TECH).
Results: ECL cells were enriched to more than 60%. Gastrin and carbachol stimulated histamine release in a dose-dependent manner. Concanavalin A did not stimulate histamine release from ECL cells. IL-8 also did not stimulate histaimine release. However, when IL-8 was added in the medium simultaneonsly with gastrin, IL-8 enhanced gastrin-stimulated histamine release from ECL cells by 62.7% ($P < 0.01$). IL-8 (10~50ng/ml) dose