492

Influence of Itopride On Esophageal Function in Man
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Introduction: Defective barrier function of the lower esophageal sphincter (LES), caused by a hypotonic sphincter or transient lower esophageal sphincter relaxations (TLESRs), is a major factor in the pathogenesis of gastroesophageal reflux disease (GERD). Itopride is a new prokinetic agent which combines antidopaminergic and acetylcholinesterase inhibitory actions. Previous studies suggested that itopride improves heartburn in functional dyspepsia patients, and decreases esophageal acid exposure in GERD. It is unclear whether this effect is due to motor effects of itopride on the LES. Aims: To study the effects of itopride on fasting and postprandial LES function in healthy subjects. Materials and methods: twelve fasted healthy volunteers (5 males; 32.6±2.0 years) underwent three esophageal sleeve manometry studies after 3 days premedication with itopride 50 mg, itopride 100 mg or placebo t.i.d. Drug was administered after 30 minutes and a standardized meal was administered after 90 minutes, with measurements continuing to 120 minutes postprandially. Throughout the study, 10 wet swallows were administered at 30-minute intervals, and gastrointestinal symptoms were scored on 100 mm visual analogue scales (VAS) at 10-minute intervals. Results: Both doses of itopride significantly decreased intragastric pressures compared to placebo (respectively 16.0±1.3 and 17.3±1.5 vs. 20.4±1.7 mm Hg, both $p<0.05$). Compared to placebo, the 50 mg dose of itopride was associated with a lower LES pressure before the meal (17.3±3.0 vs. 11.8±1.6 mmHg, $p<0.05$), but postprandial LES pressures did not differ from placebo for any time points for both doses of itopride. Swallow-induced relaxations and the amplitude or duration of peristaltic contractions were not altered by both doses of itopride, at all time points. The 50 mg dose of itopride inhibited TLESRS compared to placebo (TLESRs total 1.7±0.7 vs. 3.3±0.5, $p=0.03$; preprandially 0.4±0.3 vs.1.3±0.3, $p=0.04$; postprandially 1.3±0.4 vs. 2.0±0.4, $p=0.16$). The 100 mg dose did not significantly alter the rate of TLESRs before or after the meal. Conclusions: Itopride 50 mg inhibits TLESRs without significantly affecting esophageal peristaltic function or LES pressure. Both doses of itopride decrease intragastric pressures. Identifying the nature and location of the receptors involved in this effect of itopride requires additional studies. Our observations support further studies with itopride in GERD.

493

The Prophylactic Effect of STW 5 in An Acute Model of Esophagitis in Rats
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Gastro-esophageal reflux is a common gastrointestinal complaint associated with a variety of functional disorders of the stomach, including functional dyspepsia, where STW 5, a multi-herbal medicinal preparation, has been successfully used to alleviate symptoms including heartburn [1, 2]. The present study was aimed at investigating the effect of STW 5 in an experimental model of esophagitis, with a view of providing further pharmacological evidence for its therapeutic usefulness. Esophagitis was induced in male Wistar rats which had been fasted for 18 h. The animals were anaesthetized and a ligature was performed between the fore-stomach and corpus as well as between stomach and pylorus in order to help induce inflammation of the oesophageal mucosa within the ensuing few hours [3]. Four hours later, the rats were sacrificed and the ulcerative area of the esophageal mucosa was measured. Lipid peroxidation, myeloperoxidase (MPO) activity, and the levels of TNFα and IL-1B were also determined in the esophageal tissue. In addition, tissue samples were fixed in formalin and examined histopathologically after H & E staining. To test the activity of STW 5 the rats were treated orally with the drug for 5 successive days in dose levels ranging from 0.2 to 2 ml/kg. Pantoprazole (5 mg/kg) was used as a reference standard. Three hours after the last dose of the test drugs the animals were anaesthetized and ligated as described [3]. Control ligated animals showed marked esophagitis, measured as the ulcerative area of the esophageal mucosa. STW 5 led to a significant dose-dependent reduction of the ulcerative area as well as to a marked decrease in the number of animals showing ulcer perforations. The effect was comparable to that of pantoprazole. MPO activity and lipid peroxidation were significantly raised in control ligated animals but these high levels were dose dependently reduced by STW 5 until normalized by the 2 ml/kg dose. TNFα and IL-1B levels were markedly raised in control ligated rats but were dramatically reduced back to normal by STW 5, an effect even superseding that of pantoprazole, thereby substantiating the anti-inflammatory activity of the drug. The effect on the biochemical parameters correlated well with the observed macroscopical effects. These effects were also confirmed histopathologically. The results show that the beneficial effect of STW 5 in heartburn and other acid related symptoms in functional dyspepsia could in part result from an anti-inflammatory effect on the esophageal mucosa. 1. Gundermann et al. (2004) MMW-Fortschr Med 146:33/34. 2. Madisch A. et al. (2007) Gut, 56 III:A336. 3. Yamato M et al. (2005) Digestion 72:109-118

494

Health-Related Quality of Life in Patients with Gastroesophageal Reflux Disease Under Routine Care - A 5-Year Follow-Up from the Progerd Study
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Gastroesophageal reflux disease (GERD) is a common disease associated with substantial reductions in health-related quality of life (HRQL). The aim of this study was to describe patterns of change in HRQL during 5 years of follow-up in a large population of GERD patients under routine care. Methods. In 2000, a total of 6215 GERD patients were enrolled in the Progression of GERD (ProGERD) study. During follow-up, patients received any medication considered necessary for the treatment of GERD. HRQL was assessed yearly using the generic Short-Form 36 (SF-36; low score=worse health state) and the disease-specific Quality of Life in Reflux and Dyspepsia (QOLRAD; low score=worse health state) questionnaires. Associations between patient characteristics and changes in HRQL were analyzed by multiple logistic regression models. Results. After 5 years, data on HRQL were available for 4597 (74%) patients. Both generic and disease-specific HRQL improved from baseline and remained well above baseline levels in the following years. Clinically meaningful improvement of mean scores for QOLRAD domains of emotional distress, sleep disturbance, food/drinking problems, and vitality was observed in more than 60% of evaluable patients. A clinically relevant decrease in QOLRAD scores was reported by only 3% to 5% of patients. According to multivariate analysis, the latter deterioration of HRQL was associated with a higher reflux symptom load and the presence of night-time heartburn. Conclusion. A clinically relevant improvement of HRQL, as determined by the QOLRAD questionnaire, was observed in more than 60% of GERD patients over a 5-year period of routine clinical care. Only a small minority of the ProGERD population reported a clinically relevant decrease in HRQL, which was most strongly associated with night-time heartburn.

495

WITHDRAWN
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Background. Proton pump inhibitors (PPIs) inhibit the function of the gastric HKATPase and are widely used to relieve symptoms in patients with gastroesophageal reflux disease. Recent epidemiological studies have shown that the use of PPI is associated with an increased risk of hip fracture in humans, but a causal relationship has been questioned. In the present study we have investigated the skeletal phenotype in HKATPase beta-subunit knockout (KO) female mice. Methods. Skeletal parameters were determined in 6 and 20 months old KO mice and in wild type controls (WT). Blood samples were collected by puncture of vena cava at the day of sacrifice. Plasma gastrin levels were analyzed by RIA. Whole body bone mineral density (BMD), bone mineral content (BMC) and body composition were measured by dual energy X-ray absorptiometry (DXA) before sacrifice. Excised femurs were examined with µCT analyses of proximal, middle and distal shafts and cortical BMD, trabecular BMD, cortical volume and trabecular thickness were measured. Mechanical properties and break force were examined by a three point bending test. P-values <0.05 were considered significant. Results. Total body weight did not differ between KO and WT mice, neither at age 6 nor 20 months. Plasma gastrin levels were significantly higher in KO mice compared to WT both at the age of 6 months (73.5 vs. 11.0 pM) and 20 months (46.2 vs 10.6 pM). Measured by DXA the KO mice had lower whole body BMC at 6 months (0.53 vs. 0.59 g) and at 20 months (0.49 vs 0.74 g) compared to WT as well as lower BMD at 6 months (0.068 vs 0.072 g/cm2) and 20 months (0.067 vs 0.077 g/cm2). Mechanical strength was significantly reduced in KO mice at the age of 20 months (6.7 vs 17.9 N). Cortical BMD, trabecular BMD, cortical volume and trabecular thickness measured by µCT were significantly reduced in 20 months old KO mice. There was also a reduction in cortical intersection surface and cortical bone surface in KO mice. Conclusion. HKATPase beta-subunit knockout mice have decreased BMC and BMD measured by DXA as well as lower volumetric density measured by µCT. The KO mice also exhibit deteriorated bone microarcitecture and decreased mechanical bone strength. Whereas the mechanism is uncertain, the present findings suggest a causal relationship between long-term PPI use and an increased risk of fractures observed in humans.

496

Matrix Metalloproteinase-9 Regulates Intestinal Cell Differentiation By Activating Notch-1
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Background and purpose: We recently showed that MMP-9, a zinc-dependent protease, plays a role in intestinal goblet cell differentiation. MMP-9-/- mice have increased goblet cells and are protected from colitis and the temporal expression of MMP-9 and notch intracellular domain (NICD), a transcription factor involved in intestinal cell fate determination, inversely correlated with MUC-2 expression in both mice as well as in intestinal epithelial cell lines. Notch-1 is a type 1 transmembrane protein that undergoes two sequential proteolytic cleavages to release NICD after binding to its ligand. The protease(s) involved in its cleavage in the intestine is not known. The purpose of our study was to examine whether MMP-9 cleaves Notch-1 and activates downstream signaling pathways such as Hes-1. Methods Used: CHO cells transfected with MMP-9 and/or various c-myc tagged Notch-1 deletion constructs were used for *In Vitro* studies. Hes-1 luciferase constructs were used to determine the effect of MMP-9/NICD on the transcriptional activation of Hes-1. MMP-9, NICD and Hes-1 expressions were determined by Western blot and/or immunohistochemistry. Transfection efficiency was verified by measuring MMP-9 expression in transfected cells. Wild type (WT) and MMP-9-/- mice were used for *In Vivo* studies. Results: Increased expression of NICD and Hes-1 was found in cells co-transfected with MMP-9 and the truncated Notch-1 construct retaining the ectodomain cleavage site compared to the cells co-transfected with vector/MMP-9 and the full-length Notch-1 construct. An eight fold increase in hes-1 tagged luciferase activity was found in cells co-transfected with MMP-9 and truncated Notch-1 having the ectodomain cleavage site compared to vector or full length Notch-1 transfected cells. Consistent with the *In Vitro* data,MMP-9-/- mice demonstrate significantly reduced NICD and Hes-1 compared to WT mice and had significantly increased number of goblet cells in the colon. Conclusions: Our data suggest that MMP-9 regulates goblet cell differentiation through the activation of the Notch pathway by cleaving Notch-1 at the ectodomain cleavage site. MMP-9 is unable to cleave full-length Notch-1, suggesting that another protease may play a role in partially cleaving notch prior to cleavage by MMP-9. Together, our data demonstrate that MMP-9 plays a physiological role in goblet cell differentiation by cleaving Notch-1. We speculate that aberrant expression of MMP-9 in colitis may modulate processes such as wound healing that require appropriate epithelial cell differentiation.