CAAA

Oral Presentation

Rising Star symposia - South Hall (Room 3)

Monday September 27 2004 15.45-17.15

Abstract:

Citation: A1

BILE SALT TRANSPORTERS: MOLECULAR CHARACTERIZATION FUNCTION AND REGULATION IN HEALTH AND DISEASE

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Bile is primarily formed at the level of hepatocytes by uptake and excretion of bile salts cholesterol phospholipids bilirubin and other biliary constituents. This is accomplished by highly specialized uptake systems and efflux pumps. Hepatocanalicular bile is then further modified by the bile duct epithelium. Expression of hepatobiliary transport systems is regulated by ligand-activated nuclear receptors which result in feedforward stimulation or feedback inhibition of gene expression by bile salts lipids and bilirubin. In addition hepatobiliary excretory function also underlies an intensive post-transcriptional regulation by second messenger systems and protein kinases which modulate targeting of transporters to the cell membrane and can directly modify transport proteins (e.g. phosphorylation).

Hereditary and acquired transport defects can result in cholestasis. Examples include progressive familial intrahepatic cholestasis benign recurrent intrahepatic cholestasis Dubin-Johnson syndrome cystic fibrosis and subtypes of intrahepatic cholestasis of pregnancy. Acquired cholestasis is also associated with impaired expression and function of hepatic uptake and excretory systems for bile salts and other organic anions (e.g. bilirubin) changes which may maintain and contribute to cholestasis and jaundice. Moreover adaptive transporter changes such as induction of alternative efflux pumps in liver and kidney may help to limit hepatic accumulation of potentially toxic biliary constituents in cholestasis by providing alternative escape routes.

These molecular changes are not only relevant for a better understanding of the pathophysiology of liver diseases but may also represent important targets of pharmacotherapy. Drugs (e.g. ursodeoxycholic acid steroids fibrates rifampicin) used to treat cholestatic liver diseases and pruritus may counteract cholestasis via stimulation of defective transporter expression and function. In addition therapeutic strategies may be aimed at supporting and stimulating adaptive rescue pathways (e.g. alternative detoxifcation pathways and elimination routes for bile salts) in

cholestasis. Novel therapeutic strategies may be aimed at nuclear receptors and their target genes involved in bile salt and lipid transport and metabolism.

Reference: Trauner M Boyer JL. Bile salt transporters: molecular characterization function and regulation Physiological Reviews{}2003; 83: 633-671.

Reference: Arrese M. Trauner M. Molecular aspects of bile formation and cholestasis. Trends in Molecular Medicine 2003; 9:558-564.

CAAB

Oral Presentation

Rising Star symposia - South Hall (Room 3)

Monday September 27 2004 15.45-17.15

Abstract:

Citation: A1

FACTORS INFLUENCING THE OUTCOME OF ANTI-TUMOR NECROSIS FACTOR (INFLIXIMAB) TREATMENT IN CROHN'S DISEASE

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INTRODUCTION: The chimeric antibody to TNF-a infliximab is very efficacious in the majority of patients with refractory luminal or fistulizing Crohn's disease. However about 30% of patients have consistently been found to be resistant to infliximab therapy. Moreover not all other patients are ``full'' responders.

AIMS & METHODS: We therefore aimed at identifying predictors of response (clinical biological or genetic) to better select candidates for infliximab treatment and to avoid exposure and possible toxicity in patients who will not benefit from this expensive therapy.

RESULTS: We prospectively studied a cohort of 240 CD patients and performed logistic regression and decision tree analysis for demographic and clinical predictors of response. Young age (OR 1.03 95%CI 1.01-1.06 p=0.018) isolated colitis (p= 0.046; OR 1.91 95%CI 1.01-3.56) and concomitant immunosuppressive treatment (p=0.0022; OR 2.67 95%CI 1.43-5.02) were positively correlated with response. We further showed that the presence of biologically active inflammation before treatment as witnessed by increased CRP (>5 mg/l) is associated with better response (76%) as compared to patients with a normal CRP (<5 mg/l) before treatment (46%; p=0.004; OR 3.85; 95%CI 1.59-9.10). Patients expressing pANCA antibodies had tendency of lower response a finding which was previously also reported by Taylor et al. Other predictors of response that have been reported are non-stricturing disease and non-smoking. We among others have studied multiple genetic polymorphisms in the TNF TNF receptor and in the NOD2/CARD15 gene but could not demonstrate an association with infliximab outcome. We did report an association however between the FcG receptorIIIa-158 polymorphism and response to infliximab. In a cohort of 200 CD patients the decrease in CRP was significantly higher in −158V/V patients compared to F carriers (p=0.0078) and a biological response was observed in 100% of the V/V patients compared to 69.8% in F carriers (p=0.0002; OR 1.43; 95%CI 1.27-1.61). Also variants in the Fas ligand gene at position −843 contribute to infliximab outcome: presence of the Fas ligand −843C allele was associated with a better clinical response (74.1%) in

a cohort of 204 treated patients as compared to the response seen in −843GG patients (38.1%; p=0.002; OR=9.10; 95%CI 1.79-12.50). Interestingly concomitant azathioprine was able to overcome the low response observed in the GG genotype of this polymorphism.

CONCLUSION: A young age concomitant immunosuppressive treatment non-smoking non-stricturing disease and colonic disease are all clinical factors that seem associated with a favourable response to infliximab. Genetic associations were noted with both the FcG receptorIIIa and with the Fas ligand gene. More extensive studies on genetic predictors together with the current knowledge will help to optimise infliximab treatment.

CAAC

Oral Presentation

Rising Star symposia - South Hall (Room 3)

Monday September 27 2004 15.45-17.15

Abstract:

Citation: A1

INHIBITION OF PROGRESSING PRIMARY ESOPHAGEAL PERISTALSIS BY PHARYNGEAL WATER STIMULATION IN HUMANS

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INTRODUCTION: Sensory impulses initiated from the pharynx exert various effects on the deglutitive apparatus. They have an inhibitory effect on the lower esophageal sphincter but an excitatory effect on the upper esophageal sphincter. The aim of this study was to systematically investigate the effect of pharyngeal sensory impulses evoked by water stimulation on the progressing esophageal peristalsis.

AIMS & METHODS: Sixteen healthy young volunteers were studied in the supine position. The presence of normal peristalsis was verified. Esophageal peristalsis was recorded 3 6 9 12 15 and 18 cm above the lower esophageal sphincter. Pharyngeal stimulation was performed by injecting a predetermined threshold volume into the pharynx 2 cm above the upper esophageal sphincter directed posteriorly. The injections were timed to coincide with the arrival of the peristaltic wave induced by dry swallows at respective recording sites.

RESULTS: Injection of the threshold volume (0.5 ± 0.1 mL) stopped the progression of peristalsis at both the striated and smooth muscle esophagus. Topical pharyngeal anesthesia blocked this inhibitory effect ($P < 0.01$).

CONCLUSION: Sensory impulses initiated from the pharynx evoked by water injection inhibit the progression of primary esophageal peristalsis. Although the clinical significance of these findings is not determined they may explain the mechanism of some of the failed esophageal peristalsis.

CAAD

Oral Presentation

Rising Star symposia - South Hall (Room 3)

Monday September 27 2004 15.45-17.15

Abstract:

Citation: A1

POLYCYSTIC LIVER DISEASE: FROM CLONING OF THE GENE PRKCSH TO CHARACTERIZATION OF THE PROTEIN: HEPATOCYSTIN

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Polycystic liver disease (PCLD MIM 174050) is a dominantly inherited condition characterized by the presence multiple liver cysts of biliary epithelial origin. This condition is distinct from autosomal dominant polycystic kidney disease type 1 (ADPKD-1 MIM 173900) and type 2 (ADPKD-2 MIM 173910). Both of these disorders may be complicated by polycystic liver disease but renal involvement is absent in PCLD. We carried out fine mapping and established linkage to marker D19S581 (Z max= 9.65; ±e8=0.01) in three large Dutch PCLD pedigrees. Sequence analysis in individuals with PCLD revealed a splice-acceptor site mutation (1338-2A>G) in {PRKCSH} a 15 kb transcript that segregated completely with the disorder in these families. This splice-acceptor site mutation causes retention of intron 15 and generates a premature stop codon eliminating the C terminal end of the protein. This finding was confirmed in other families and mutational analysis of the {PRKCSH} gene has so far demonstrated a total of 4 different truncating mutations (splice site; deletions) in PCLD patients from Dutch and Finnish descent. The {PRKCSH} transcript denoted by us as hepatocystin is predicted to encode for a 59 kDa protein with an amino-terminal signal sequence for translocation across the endoplasmic reticulum (ER) membrane a low-density lipoprotein class a (LDLa) domain two putative Ca^{2+}-binding EF hands and a ER targeting sequence. Preliminary evidence suggest that hepatocystin acts as the beta subunit of glucosidase II an ER resident enzyme involved in carbohydrate processing and quality control. As a step towards elucidating the involvement of hepatocystin in PCLD we have undertaken a biochemical and morphological characterization of both normal and mutant forms of hepatocystin. The results of our studies indicate that normal hepatocystin is an ER protein that associates with the catalytic alpha subunit of glucosidase-II. The 1338-2 A>G truncating mutation produces a protein that is not retained in the ER but is being secreted into the medium probably due to deletion of the ER targeting sequence. Also it does not assemble with the glucosidase-II alpha subunit. Notably mutant hepatocystin is absent in PCLD liver tissue despite detectable mRNA. Probably as a consequence liver and Epstein Barr Virus transformed lymphocytes from the patients contain reduced levels of both normal

hepatocystin and glucosidase-II alpha subunit and levels are even lower in hepatic cysts from PCLD patients. These findings are most consistent with a role of hepatocystin in carbohydrate processing and quality control of newly synthesized proteins in the ER. Therefore reduced ER processing of some key regulator of cell proliferation may underlie PCLD.

CAAE

Oral Presentation

Rising Star symposia - South Hall (Room 3)

Monday September 27 2004 15.45-17.15

Abstract:

Citation: A1

COX-2 AND COLORECTAL CARCINOGENESIS

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The inducible isoform of cyclooxygenase (COX) COX-2 plays an important role in the early stages of intestinal tumorigenesis in rodents. However the mechanism(s) underlying the pro-tumorigenic activity of COX-2 during colorectal carcinogenesis remain to be elucidated. Work in my laboratory has investigated the expression and function of COX-2 in intestinal adenomas (or polyps) as this lesion represents a relevant target for chemoprevention of colorectal cancer.

COX-2 is localized predominantly to stromal macrophages and fibroblasts (but not dysplastic epithelial cells) in human sporadic colorectal adenomas and adenomas from the $Apc^{Min/+}$ mouse model of familial adenomatous polyposis. Stromal cell Cox-2 promotes angiogenesis in murine intestinal adenomas and macrophage COX-2 expression correlates with microvessel density in human colorectal adenomas. There is also evidence from separate in vitro and in vivo models that COX-2 can have direct paracrine activity on intestinal epithelial cells. The pro-tumorigenic activity of COX-2 is at least in part explained by prostaglandin (PG) E_2 which acts predominantly via EP2 and EP4 receptors during intestinal tumorigenesis.

At later stages of colorectal carcinogenesis COX-2 becomes localized to epithelial cells as well as the stromal compartment of colorectal cancers. The factor(s) responsible for stage-specific stromal and epithelial cell COX-2 expression remains unknown. COX-2-expressing stromal cells in $Apc^{Min/+}$ mouse adenomas do not express inducible nitric oxide synthase implying a specific (possibly M2) activated macrophage phenotype. RAS mutation has been postulated as necessary for up-regulation of COX-2 protein in intestinal epithelial cells. However expression of transgenic RAS(G12V) does not lead to COX-2 protein localization in dysplastic epithelial cells of Apc^{1638N} mouse adenomas.

Understanding of the mechanisms controlling cell type-specific COX-2 expression may lead to development of therapeutic strategies to inhibit COX-2 expression rather than activity in colorectal neoplasms. Delineation of signalling events downstream of COX activity during

colorectal carcinogenesis may lead to derivation of other chemoprevention agents alongside selective COX-2 inhibitors. This is important as a proportion of adenomas do not contain COX-2 and PG signalling via COX-1 (which has similar enzymatic activity to COX-2) is increasingly recognised to contribute to intestinal tumorigenesis.

CAAF

Oral Presentation

Rising Star symposia - South Hall (Room 3)

Monday September 27 2004 15.45-17.15

Abstract:

Citation: A2

HYDROXYACID OXIDASE 1: A LIVER SPECIFIC PEROXISOMAL ENZYME AND ITS REGULATION BY OXIDATIVE STRESS

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Hydroxy acid oxidase 1 (Hao1) is a liver-specific peroxisomal enzyme that oxidizes glycolate to glyoxylate with concomitant production of H2O2. In Hao1 mRNA is present an iron responsive element (IRE) homologous to the sequence recognized by iron regulatory proteins (IRP) key regulators of iron homeostasis but the involvement of the IRE/IRP pathway in Hao1 regulation is still unclear. To asses wether iron controls Hao1 espression in vivo we analyzed Hao1 mRNA levels in iron-rich and depleted rat livers. Hao1 mRNA content was markedly reduced below control levels in the liver of rats with chronic dietary iron overload which showed decreased IRP activity and higher ferritin expression as expected but also induction of heme oxygenase (HO-1) a marker of oxidative damage. Hao1 mRNA levels were not significantly altered in the liver of rats administered doses of iron sufficient to induce ferritin expression and to repress IRP activity but not to activate HO-1 as well as in the liver of iron deficient rats. These observations were not consistent with a postranscriptional downregulation of Hao1 by iron through the IRE/IRP pathway and suggested an effect of reactive oxygen species (ROS). Indeed a marked decrease of Hao1 mRNA was observed in the liver of rats subjected to oxidative stress induced by either glutathione depletion or postischemic reperfusion. Nuclear run on analysis demonstrated an effect of ROS at the transcriptional level. In conclusion downregulation of Hao1 expression during oxidative stress may provide a mechanism to prevent excessive H2O2 formation in liver peroxisomes and may represent the prototype of a poorly recognized but potentially relevant response to oxidative injury involving downregulation of ROS-producing enzymes.

CAAG

Oral Presentation

Rising Star symposia - South Hall (Room 3)

Monday September 27 2004 15.45-17.15

Abstract:

Citation: A2

THROMBOPOIETIN AND HEMATOPOIETIC GROWTH FACTORS IN LIVER DISEASE

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{Pathophysiology of hematologic abnormalities in liver disease:} Advanced chronic liver disease is accompanied by derangements of the hematopoietic system commonly termed hypersplenism. Studies into the role of hematopietic growth factors have revealed not only increased destruction of blood cells but also impaired production mostly due to relative growth factor deficiency. Most notably studies in liver transplant patients have shown thrombpoetin (TPO) deficiency as one of the important mechanisms for thrombocytopenia in liver disease since TPO is produced mostly by the liver.

Erythropoietin (EPO)-production is also blunted in advanced cirrhosis and additional myelosuppression has been attributed to chronic HBV and HCV-infection.

{Hematopoietic and hemostatic side effects of antiviral therapy in hepatitis C:} Combination antiviral therapy causes pancytopenia due to either myelosuppression (platelets leukocytes) or hemolysis. While EPO response to haemolytic anemia seems to be adequate the TPO-response to thrombocytopenia seems to be impaired or in cirrhotics even missing at all. IFN-therapy on the other hand causes upregulation of vWF-Ag which counteracts the hemorrhagic diathesis caused by thrombocytopenia and leads to normalisation of the in-vitro bleeding time (PFA-100) in non-cirrhotics.

{Use of hematopoietic growth factors in liver disease:} Use of growth factors despite significant abnormalities has not been widely used for patients with advanced stage liver disease. Epo and IL-11 has been used to counteract thrombocytopenia with moderate effect (EPO) or significant side-effects (IL-11). TPO is not available for clinical use at the moment. Recombinant EPO causes significant rises in platelet count and platelet reactivity in advanced stage cirrhotics.

{Therapeutic interventions for cytopenias during antiviral therapy (basic and clinical aspects):} In contrast to the situation in advanced stage cirrhosis recombinant EPO used concomitantly with combination antiviral therapy causes an increase in TRAP-induced P-selectin expression and less

anemia but has litte influence on platelet count or platelet reactivity possibly due to a lack of effect on vWF-Ag expression.

G-CSF usage is usually effective to counteract the leucopenia during antiviral therapy but its usefulness has not been established due to the low incidence of infectious complications during antiviral therapy.

Anemia during antiviral therapy can be alleviated through the use of recombinant EPO but whether this positively impacts SVR in patients with chronic hepatitis C has not been shown to date. The effects of EPO on the correction of anemia are fairly modest compared to other indications with a high proportion of patients not reasonably responding to EPO at all. On a molecular level IFN as well as TPO and EPO use signalling through the Jak-Stat pathway. IFN induces suppressors of cytokine signalling (SOCS) molecules which can effectively inhibit EPO signalling and possibly also TPO signalling leading to a poor growth factor response in these patients. On another level IFN could also interfere with transcriptional regulation of TPO expression by inducing alterative promoter usage and production of transcripts with very different translation efficacy.

Complete elucidation of these mechanisms will help to decide whether clinical usage of these expensive drugs can be expected to sufficiently impact our patients to warrant their usage.

CAAH

Oral Presentation

Rising Star symposia - South Hall (Room 3)

Monday September 27 2004 15.45-17.15

Abstract:

Citation: A2

IMMUNE MODULATION AND ANTIVIRAL THERAPY FOR CHRONIC HEPATITIS B VIRUS INFECTION

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Combining the virus suppressive effect of lamivudine with immune modulatory effects of interferon alpha could theoretically enhance treatment response. Preliminary results from our group showed that interferon-lamivudine combination therapy gives a stronger initial virus suppression than monotherapy with either lamivudine or interferon. Previous studies on standard interferon combined with lamivudine showed conflicting results. Problems in the design of these studies and the lack of data on sustained off-treatment response prevent a definitive conclusion concerning the efficacy of combination therapy of interferon and lamivudine. The recent introduction of pegylated interferons (peginterferons) in the treatment of hepatitis C has led to greater treatment efficacy than that achieved with standard interferon and preliminary studies have been carried out in the treatment of chronic hepatitis B.

In a global randomized controlled study 266 patients with HBeAg-positive g per week and ±b5-2b 100 {\f1 a} chronic hepatitis B were randomized to peginterferon g per week and placebo. All ±b5lamivudine 100 mg per day versus peginterferon 100 patients were HBV-DNA positive (hybridization assay) and had ALT values more than twice ULN at baseline. Treatment was given for 52 weeks and post-treatment follow-up lasted 26 weeks. The dose of peginterferon was reduced to 50 micrograms at week 32. At the end of follow-up equal response rates (serum HBeAg clearance) were found in both treatment groups. More patients on combination therapy exhibited an HBeAg response initially at the end of treatment but relapsed during follow-up. Similar response patterns were seen when response was assessed by HBV DNA suppression and change in ALT levels. Major predictors for response were HBV genotype and ALT values. About 80% of the patients completed the therapy on full dose. Dose reduction was 10% in the first 8 weeks and another 10% between week 8 and 26. Ten percent of patients prematurely discontinued peginterferon mainly between week 0 and 32. In conclusion peginterferon is effective and well tolerated for chronic hepatitis B. Combination therapy with peginterferon and lamivudine is not superior to peginterferon monotherapy.

AAAI

Oral Presentation

Novel methods for the diagnosis of small bowel disease - South Hall (Room 3)

Monday September 27 2004 11.00-12.30

Abstract: OP-G-1

0 Citation: Gut 2004; 53 (Suppl VI) A2

CAPSULE ENDOSCOPY IN DIAGNOSIS OF SMALL BOWEL CROHN'S DISEASE: A PROSPECTIVE MONOCENTRIC STUDY WITH COMPARISON TO MRI AND ENTEROCLYSIS

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INTRODUCTION: Diagnosis of small bowel Crohn's disease (CD) has been impaired by the limited endoscopic visualization of the intestinal mucosa. To evaluate modern diagnostic imaging methods we performed a controlled prospective and blinded trial comparing diagnostic potential of Capsule Endoscopy (CE) magnetic resonance imaging (MRI) and conventional enteroclysis (SBE) in the small bowel.

AIMS & METHODS: Eighty-one patients were screened for eligibility by a standard diagnostic work-up including physical examination laboratory investigations microbiological stool tests abdominal ultrasonography ileo-colonoscopy and upper endoscopy. In twenty-nine patients diagnosis could be established with these diagnostic means and no further testing was indicated. In the remaining 53 patients small bowel imaging was performed by CE MRI and enteroclysis. To exclude bowel strictures abdominal ultrasonography and either enteroclysis or MRI were performed before CE. For CE all patients were required to drink 2000ml of a bowel purgative before the investigation and Simethicone was given prior to capsule ingestion.

RESULTS: Of the 53 patients investigated 28 presented with established and 25 with suspected CD. In the latter a diagnosis of CD could be confirmed in 14 cases (56%) after complete diagnostic work-up. Inflammatory small bowel lesions typical for CD were seen by CE in 12 of 13 cases. In fourteen patients high grade bowel stricture was detected eight of whom had been operated 3 to 14 years (mean: 6.2 years; SD: 4.10) earlier. Results for suspected CD are shown in table 1. In established CD CE detected 13/14 (92.9%) MRI 11/14 (78.6%) and SBE 4/12 (33.3%) of small bowel lesions. CE was exclusively diagnostic for the final diagnosis in suspected CD in three patients and in deteriorating CD in two patients.

TABLE 1. Sensitivity and specificity for small bowel lesions in suspected CD (N=

CE MRI SBE none Sensitivity 12/13 (92.3%) 10/13 (76.9%) 3/9 (33%) Specificity 11/11 (100%) 8/10 (80%) 5/6 (83%)

CONCLUSION: CE is most sensitive in detection of even subtle mucosal lesions of small bowel CD but is limited by stricturing disease. MRI represents a complementary means to CE and SBE seems to be replaceable by CE and MRI in most cases.

AAAJ

Oral Presentation

Novel methods for the diagnosis of small bowel disease - South Hall (Room 3)

Monday September 27 2004 11.00-12.30

Abstract: OP-G-2

0 Citation: Gut 2004; 53 (Suppl VI) A2

CORRELATION OF FINDINGS IN MR-ENTEROCLYSIS AND CAPSULE ENDOSCOPY IN THE SMALL BOWEL IN PATIENTS WITH CROHN'S DISEASE

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INTRODUCTION: MR-enteroclysis (MRE) appears to be a promising new technique in the assessment of small bowel involvement in Crohn's Disease (CD). Due to limited endoscopic access no data were available on the accuracy of MRE in the detection of small bowel involvement. Wireless capsule endoscopy (CE) can detect luminal signs of CD and may serve as control. Therefore we applied CE in a prospective pilot study in patients with CD and small bowel involvement detected by MRE.

AIMS & METHODS: 25 patients with symptoms of small bowel involvement and proven CD (colon or terminal ileum) were routinely examined by MRE. MRE was performed with complete small bowel distension by filling through a nasojejunal tube and spasmolytic agents. To enable comparison of the MR and CE data three segments of similar length were defined i.e. upper mid and lower small bowel. In MRE the full small bowel length was divided into three equal parts. Wall thickening (>3mm) enhanced uptake of contrast media and luminal narrowing were considered as positive results. In CE the complete recording time interval between the first duodenal picture after ligament of Treitz and the last picture of the terminal ileum was divided into three equal parts. Mucosal lesions defined as aphthous ulcers fibrinous lesions and pseudopolyps were considered as positive results. Patients with signs of segmental involvement in the MRE proximal to the terminal ileum were than examined by CE.

RESULTS: 10 patients with positive MRE underwent CE. During battery life time CE reached the coecum in 5 patients the terminal ileum in 3 patients and the mid ileum in 1 patient. All capsules were excreted naturally within 5 days without side effects. CE showed involvement of the small bowel proximal to the terminal ileum in 21 segments whereas MRE detected involvement in only 12 segments. 10 segments of MRI-detected segment were approved by CE. In 1 patient CE correlated exactly with the MR findings. In 5 patients CE showed involvement of all 3 segments whereas MRE detected only two (n=2) or one (n=3) segments. In 2 patients CE

showed involvement of 2 whereas MRE detected involvement in one segment. In 1 patient CE showed no involvement in any segment MRE detected involvement in 1 segment.

CONCLUSION: CE seems to be more accurate than MRE in the detection of mucosal affection in the small bowel in patients with Crohn's Disease MRE may underestimate the rate of small bowel involvement. In patients with symptoms of small bowel involvement lesions proximal to the terminal ileum are frequent.

AAAK

Oral Presentation

Novel methods for the diagnosis of small bowel disease - South Hall (Room 3)

Monday September 27 2004 11.00-12.30

Abstract: OP-G-3

0 Citation: Gut 2004; 53 (Suppl VI) A3

SHOULD CAPSULE ENTEROSCOPY BE THE FIRST LINE IMAGING EXAMINATION IN PATIENTS WITH SUSPECTED SMALL BOWEL CROHN'S DISEASE?

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INTRODUCTION: Diagnosis and adequate therapy of small bowel Crohn's disease (SBCD) are frequently delayed due to the limitations associated with current routine imaging techniques of the small bowel (SB).

AIMS & METHODS: Our aim was to investigate and compare the diagnostic value of Given±ae capsule enteroscopy barium enterography push enteroscopy and ileoscopy in SBCD. This prospective and partly blinded study included 53 consecutive patients (40 women and 13 men mean age 36 years range 14-62) with suspected (61%) or previously diagnosed (39%) and clinically active CD.

RESULTS: 47 patients completed all 4 examinations 5 patients with SB stricture detected on barium enterography and one patient with ischemic enteropathy were excluded. SBCD were detected by one or more methods in 25 (53%) of the 47 patients. Capsule enteroscopy confirmed all cases with SBCD identified by barium enterography push enteroscopy and ileoscopy except in 3 cases in which the capsule did not pass through the SB during the examination. Capsule enteroscopy identified 4 additional patients with CD and detected more extended SBCD in 6 (24%) patients compared to the other methods. The sensitivity of capsule enteroscopy for detecting SBCD was 0.88 whereas the sensitivity of ileoscopy barium enterography and push enteroscopy was only 0.68 0.24 and 0.16 respectively.

CONCLUSION: Our study shows that capsule enteroscopy is a safe well-tolerated and more sensitive imaging technique for detecting Crohn's lesions in the SB compared to barium enterography push enteroscopy and ileoscopy. Capsule enteroscopy should be considered as a first line imaging examination in patients with suspected non-stricturing SBCD.

AAAL

Oral Presentation

Novel methods for the diagnosis of small bowel disease - South Hall (Room 3)

Monday September 27 2004 11.00-12.30

Abstract: OP-E-4

0 Citation: Endoscopy 2004; 36 (Suppl I) A3

USE OF THE NEW DISSOLVING M2A±ae PATENCY CAPSULE BEFORE VIDEO CAPSULE ENDOSCOPY IN PATIENTS WITH KNOWN SMALL BOWEL STRICTURES

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INTRODUCTION: Video capsule endoscopy (VCE) (Given Imaging Limited Israel) provides excellent visualisation of the small intestine is well tolerated and is safe. However one major contra-indication in using VCE is represented by intestinal stricture. Availability of non radiological methods which are able to exclude significant small bowel strictures prior to VCE would be necessary.

AIMS & METHODS: Aim was to evaluate the safety of VCE in patients with small bowel stricture in which the intestinal patency was proven by M2A±ae Patency Capsule. Twenty patients (12 female; mean age 43.8 years range 21-83) with a diagnosis of Crohn's disease (n=18) (CDAI<150) adhesive syndrome (n=1) and suspected ischemic enteritis (n=1) were included prospectively in the study protocol. In all cases a previous small bowel barium x-ray detected small bowel strictures involving the ileo-cecal valve in 5 cases and ileo-colonic anastomosis in 1. The Patency Capsule was ingested. If the Patency Capsule was excreted intact within 72 hours after the ingestion and adverse events were not observed patients were requested to perform a standard VCE to assess and confirm the possible presence of strictures or other gastrointestinal pathologies.

RESULTS: All patients swallowed the Patency Capsule smoothly. Nine out of 20 patients were not eligible for VCE: 4 patients excreted a dissolved capsule 2 did not retrieve the Patency Capsule in the stools 2 withdrew the consent and 1 experienced abdominal pain during the small bowel Patency capsule transit. The remaining 11 patients (55%) excreted the Patency Capsule after a mean transit time of 28.4 hours (SD 16.8) and swallowed the VCE. In all cases the VCE passed through the small bowel stricture and was excreted. In 10/11 cases the VCE was retrieved in the stools after a mean transit time of 36.8 hours (SD 26.7). One patient did not retrieve the VCE in the stools and the excretion was confirmed by X-Ray. The VCE showed the presence of

ulcers (n=10) cobblestone pattern (n=5) mucosal erosions (n=3) and substenotic area (n=1). No adverse event occurred. Correlation was found between the Patency Capsule and VCE transit time (Pearson rho=0.85 p=0.0015)

CONCLUSION: The M2A±ae Patency Capsule gives direct indication of functional patency even in cases with known intestinal strictures. When the M2A±ae Patency Capsule is excreted intact within 72 hours without adverse events the VCE can pass uneventfully. A discrepancy between the radiological features and intestinal patency and between the clinical and the endoscopic activity was observed. Finally the Patency Capsule transit time could predict the VCE transit time.

AAAM

Oral Presentation

Novel methods for the diagnosis of small bowel disease - South Hall (Room 3)

Monday September 27 2004 11.00-12.30

Abstract: OP-E-5

0 Citation: Endoscopy 2004; 36 (Suppl I) A3

CONTRAST ENHANCED ULTRASOUND PERFUSION STUDIES OF THE BOWEL IN PATIENTS WITH CROHN DISEASE: INITIAL RESULTS

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INTRODUCTION: Contrast enhanced ultrasound (CEUS) has been used previously in qualitative or semi quantitative studies to assess Crohn Disease (CD) activity.

AIMS & METHODS: The aim of this paper is to define the possible application of CEUS perfusion studies of the bowel to efficiently quantify CD activity.

Fifteen consecutive patients (Male: 4 Female: 11 / age: 22-55 years mean: 34 years) with a confirmed diagnosis of CD have been presently enrolled in the study group. According to clinical laboratory endoscopic and/or enteroclysis data 11 patients had active disease 3 were at a stage of disease remission and 1 was at a stage categorized as heavy fibrostenotic disease. The control group comprised of 10 individuals with no medical evidence of GI tract liver kidney heart or endocrine glands disease. Conventional B-mode sonography using both standard and high-resolution techniques was initially performed in both groups. Following the B-mode findings a CEUS perfusion study of the involved bowel segments was carried out using a second-generation ultrasound contrast agent (SonoVue Bracco) and Contrast Pulse Sequence mode on a Sequoia 512 Siemens unit. CEUS perfusion studies using the above mentioned parameters were similarly applied to the terminal ileum loop of the control group individuals. Digital video clips were recorded for 1 minute and time to contrast intensity transit curves were built. The maximum inclination of the wash-in component of the curves corresponding to perfusion rate was calculated for each individual. The presence of hyperemic vasa recta at the mesenteric bowel border was also recorded.

RESULTS: The maximum inclination values were 9.65-47.37 sec^{-1} mean: 24.41 sec^{-1} for the patients with active CD. Patients with inactive CD showed maximum inclination values of 2.27-3.94 sec^{-1} mean: 3.05 sec^{-1} whereas for the control group values were 1.83-6.10 sec^{-1} mean:

4.05 sec^{-1}. Statistically significant differences were found between the values from the active CD patients the inactive CD patients and the control group. The inactive CD individuals although very few at present showed similar perfusion values with those of the control group. Only patients with active CD showed hyperemia and increased number of the vasa recta.

CONCLUSION: Our initial data support the hypothesis that CEUS perfusion studies of the CD involved bowel segments may offer an objective tool to assess CD activity.

AAAN

Oral Presentation

Novel methods for the diagnosis of small bowel disease - South Hall (Room 3)

Monday September 27 2004 11.00-12.30

Abstract: OP-E-6

0 Citation: Endoscopy 2004; 36 (Suppl I) A3

MAGNETIC RESONANCE (MR) IMAGING CHARACTERISTICS OF MESENTERIC FISTULA IN PATIENTS WITH CROHN'S DISEASE BASED ON MR-ENTEROCLYSIS (MR-E)

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INTRODUCTION: To determine MR-imaging characteristics in MR-enteroclysis (MR-E) describing mesenteric fistula in Crohn's disease.

AIMS & METHODS: Out of 48 patients being operated for typical complications of Crohn's disease in the years 2002 and 2003 14 patients were identified to suffer from mesenteric fistula with complex small bowel and organ involvement. All patients had undergone MR-E leading to the diagnosis. MR-E was performed on a 1.5T MR scanner after trans-catheter instillation of negative intra-luminal contrast under MR-Fluoroscopy. The morphologic imaging findings of mesenteric fistula in MR-E were analyzed retrospectively by one observer blinded to the surgical results.

RESULTS: All patients showed involvement of more than one small or large bowel segment within the mesenteric fistula. 4 patients had involvement of the urinary bladder. A ``star-sign'' describing a radial arrangement of involved bowel segments and fistular tracts to organs was observed in 10/14 patients with complex fistula and could be identified as ``characteristic''. All fistular tracts presented as tubular structures with contrast medium enhancement within the mesentery.

CONCLUSION: MR-E after trans-catheter instillation is a reliable tool to depict and distinctly describe the involvement of small and large bowel segments as well as abdominal organs in complex mesenteric fistula. Typical characteristics can be found to indicate the presence of mesenteric fistula resembling a ``star-sign''.

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AAAO

Oral Presentation

Novel methods for the diagnosis of small bowel disease - South Hall (Room 3)

Monday September 27 2004 11.00-12.30

Abstract: OP-G-7

0 Citation: Gut 2004; 53 (Suppl VI) A3

EVALUATION OF CAPSULE ENDOSCOPY IN CELIAC DISEASE PATIENTS WITH ONGOING SYMPTOMS ON A GLUTEN-FREE DIET - INTERIM RESULTS OF A PROSPECTIVE BLINDED EUROPEAN MULTICENTER TRIAL

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INTRODUCTION: Celiac disease (CD) is a gluten-sensitive enteropathy with a life-long need for a strictly gluten-free diet. CD is characterized by 3 unique pathogenic factors: 1. gluten as external trigger 2. antigen-presentation via DQ2 / DQ8 and 3. mucosal (IgA) autoimmunity to tissue transglutaminase (tTG). Using oesophagogastroduodenoscopy (EGD) only proximal inspection of the small intestine is possible while capsule endoscopy (CE) allows examination of its entire length. We therefore used CE to study the extension of mucosal lesions of patients with complicated CD who did not respond to a gluten free diet.

AIMS & METHODS: We performed a prospective blinded European multicenter trial. The main group consisted of 40 patients with histologically proven proximal villous atrophy and / or positive anti-tTG antibodies and complaints despite more than 1 year of a strictly gluten free diet. 20 patients with recently diagnosed CD (positive histology and serology) not yet on a gluten-free diet served as controls. In each patient EGD with at least 4 biopsies from the descending duodenum was performed and results were compared with CE. Interim results of 31 Patients are now available (28 with complicated and 3 with recently diagnosed CD).

RESULTS: The 3 untreated celiac controls showed typical villous atrophy. In 20 of 28 of the complicated patients CE revealed mucosal alterations of the proximal and in 1/28 of the whole small intestine. In 6 of the complicated patients no mucosal atrophy was seen. Only in one patient the capsule did not pass the pylorus during recording time. In both groups a good correlation between capsule endoscopy and proximal histology was found. In most patients (20/31) main mucosal alterations were detected in the proximal part of the small intestine. No complications have been recorded and all capsules passed naturally.

CONCLUSION: Results of CE correlated strongly with the histological results of EGD. CE can help to delineate the expansion of mucosal alterations in celiac disease patients mostly with a good correlation between (proximal) histological results and CE.

AAAP

Oral Presentation

Novel methods for the diagnosis of small bowel disease - South Hall (Room 3)

Monday September 27 2004 11.00-12.30

Abstract: OP-E-8

0 Citation: Endoscopy 2004; 36 (Suppl I) A3

DOUBLE-BALLOON ENTEROSCOPY: PRACTICAL EXPERIENCE IN 24 PATIENTS

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INTRODUCTION: The small intestine known as the black box where obscure bleeding as well as various lesions occurs is uneasy to evaluate due to the length and the sharp loops. Till now various means (including push enteroscopy) have been employed to detect and manage small intestinal lesions. The diagnostic yield is however variable and depending on the clinical indication. In addition these techniques are characterised by their limitations and invasiveness.

A new insertion method of enteroscopy a double-balloon method (Fuji Photo Optical Incorporated Company) has been previously reported which enables endoscopic scrutiny of the entire small bowel with intervention capabilities. Preliminary results with this new technique are presented.

AIMS & METHODS: Between January and May 2004 24 patients (F:M = 9:15; mean age 56.3; range 29-80) with occult gastrointestinal bleeding (n=11) refractory coeliac disease (n=6) Peutz-Jegher syndrome (n=4) Crohn's disease (n=1) radiation enteritis (n=1) suspected intestinal melanoma (n=1) underwent the double-balloon technique.

RESULTS: Oral introduction of scoop took place in 21 patients and anal approach in another three patients with upper gastrointestinal surgery. Although large extent of the small intestine could be inspected in majority of patients the caecum was reached in only 2 patients (10%) when oral approach was performed. Mean duration of examination was 85±b135 minutes. Sedoanalgesia was composed of fentanyl (mean 75±b125 mcg) and midazolam (mean 12±b12 mg). Butylscopolamine or glucagon was administered if required especially when interventions were performed. Lesions detected with this technique included polyps arterio-venous malformations and mucosal changes seen in coeliac disease. Biopsy argon plasma coagulation (20 watt; 0.2L/min) snare polypectomy and tattooing of small intestine could be performed without adverse effects. While no major complications have occurred two patients described the examination as uncomfortable and one patient had post-procedural abdominal pain that resolved spontaneously within hours during observation.

CONCLUSION: Double-balloon enteroscopy is a new elegant endoscopical technique that seems promising as the endoscopist can reach undiscovered small bowel segments. Interventions in the small intestine are possible. Complications and invasiveness are minimal in this well-tolerated procedure.

AAAQ

Oral Presentation

Novel methods for the diagnosis of small bowel disease - South Hall (Room 3)

Monday September 27 2004 11.00-12.30

Abstract: OP-E-9

0 Citation: Endoscopy 2004; 36 (Suppl I) A4

THE EUROPEAN EXPERIENCE WITH DOUBLE-BALLOON ENDOSCOPY: INDICATIONS METHODOLOGY AND SAFETY

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INTRODUCTION: Double balloon endoscopy (DBE) is a technique that allows visualization biopsies and therapeutic interventions in all segments of the gastrointestinal (GI) tract. However the diagnostic and therapeutic yield of this technique have not been extensively studied.

AIMS & METHODS: Aim of the study was to evaluate the usefulness feasibility and safety of DBE in patients with small bowel disorders in four European Medical Centers (DBE-European Study Group). 62 patients (pts) (M:43 F: 19; mean age: 52 years ±b135) were investigated by DBE (EN-450P5/20 Fuji Photo Optical Co. Ltd). A total of 89 procedures were performed with 26 and 9 pts investigated only from the oral and anal route respectively and 27 pts from both the approaches. The procedure was performed with the pts under deep or light anesthesia with propophol (39 pts) or midazolam (22 pts). Indications included: obscure or occult GI bleeding (34); chronic diarrhea (5); iron-deficiency anemia (IDA) (5); refractory caeliac disease (4); abdominal pain (3); FAP (3); Crohn's disease (3); staging of GI tumors (3); Peutz-Jeghers disease (2) Gardner syndrome (1).

RESULTS: 88.5% of procedures were completed. No complications occurred. The only side effect observed was a vague abdominal pain for the following day in 3 pts. Mean time to complete the procedure from the oral and anal approach was 70±b130 min and 90±b135 min

respectively. The endoscope mean length of insertion was as far as 254±b1174 cm beyond the pylorus and 180±b1150 cm beyond the ileo-cecal valve. A diagnosis was made in 50 pts (80%): in 29 out of 33 pts with GI bleeding diagnosis (18 angiodysplasia 4 Crohn's disease 2 ulceration with substenosis 1 jejunum divertuculum 1 Meckel's diverticulum 1 neurofibroma 1 post-radiation stenosis 1 jejunum lymphoma); in 1 out 5 pts with IDA (jejunum angiodysplasia); in 3 out of 5 pts with diarrhea (1 autoimmune enteritis 1 Crohn's disease 1 multiple angiodysplasias); in 2 out of 3 pts with abdominal pain (Crohn's diasease); in 2 out of 3 pts with GI cancer (1 jejunal recurrent LHN and 1 carcinoma). Endoscopic treatment was possible in 17 pts (4 polyposis and 14 angiodysplasia).

CONCLUSION: DBE is a feasible new diagnostic and therapeutic tool for small-bowel diseases. Our data suggest that DBE is safe and does not appear to be associated with any significant adverse event. At present the best candidates for the procedure seem those with obscure-occult GI bleeding.

AAAR

Oral Presentation

Liver Disease - Basic science - Panorama Hall (Room 5)

Monday September 27 2004 11.00-12.30

Abstract: OP-G-10

0 Citation: Gut 2004; 53 (Suppl VI) A4

COPPER ACCUMULATION AND TOXICITY IN THE LIVERS OF THE WILSON'S DISEASE GENE KNOCK-OUT MICE

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INTRODUCTION: Wilson's disease (WD) is a severe genetic disorder associated with accumulation of copper in a number of tissues particularly in the liver. The affected gene in patients with WD {ATP7B} is well known; however the molecular mechanisms and cellular events leading to liver pathology in WD remain poorly understood.

AIMS & METHODS: As the first step towards in-depth analysis of the liver disease due to copper accumulation we describe morphological histochemical and biochemical changes in the liver of {ATP7B}(−/−) knock-out mice at different time points.

RESULTS: There is a biphasic character of copper accumulation in the livers of {ATP7B}(−/−) mice. Hepatic copper rises quickly and at 5-6 weeks reaches a maximum of 1.4-1.8 ±b5g/mg which is approximately 20-40 fold higher than in control animals. Copper accumulates predominantly in the cytosol where it binds to the low-molecular-weight proteins. Among organelles nuclei accumulate proportionally more copper resulting in a marked increase in nuclear size and nuclear damage. High copper concentration remains constant up to 20 weeks of age and then declines coincident with marked changes in gross liver morphology. The livers of {ATP7B}(−/−) animals become enlarged with brown and gray nodules distinct from remaining normal parenchyma. Histological changes associated with copper accumulation are very striking and depend on the stage of the disease. By 6 weeks 50% of the mice show focal to diffuse but mild necro-inflammation. At 20 weeks the changes are universal and dramatic with extreme degrees of hepatocellular injury and dysplasia foci of nodular regeneration and bile duct proliferation. Over the next 6 months a remarkable degree of recovery of large portions of the liver is accompanied by the localized occurrence of adenocarcinoma arising from the proliferating bile ducts. Initial biochemical characterization of {ATP7B}({−/−}) liver

homogenates revealed significant up-regulation of glutathione-S-transferase isoform Pi at the protein and mRNA levels.

CONCLUSION: We conclude that {ATP7B}(−/−) mice represent a valuable model for analysis of copper toxicity and regeneration in the liver.

AAAS

Oral Presentation

Liver Disease - Basic science - Panorama Hall (Room 5)

Monday September 27 2004 11.00-12.30

Abstract: OP-G-11

0 Citation: Gut 2004; 53 (Suppl VI) A4

IDENTIFICATION OF CHOLESTEROL GALLSTONE SUSCEPTIBILITY GENES FROM QUANTITATIVE TRAIT LOCUS MAPPING IN AN INTERCROSS OF PERA/EI AND DBA/2J INBRED MOUSE STRAINS AND COMBINED ANALYSIS OF INDEPENDENT CROSSES

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INTRODUCTION: We employ quantitative trait locus (QTL) mapping to identify genomic regions that harbor cholesterol gallstone susceptibility ({Lith}) genes in inbred mice. In a previous intercross of gallstone susceptible PERA and gallstone resistant I/LnJ mice we detected {Lith} loci on chromosome (Chr) 10 and Chr 17 named {Lith7} and {Lith9} respectively. Our analysis of parental strains and offspring provided evidence that the genes encoding the nuclear bile salt receptor FXR and the canalicular cholesterol transporter ABCG5/ABCG8 underlie {Lith7} and {Lith9} respectively.

AIMS & METHODS: To examine further the genetic determinants of cholesterol gallstone susceptibility we re-examined PERA mice in a QTL analysis with DBA/2 mice another gallstone resistant strain. We phenotyped 324 F_2 offspring for cholelithiasis after 8 weeks' consumption of a high-cholesterol cholic acid-containing diet. Offspring were genotyped and linkage analysis was performed by interval mapping. In addition we analysed the combined datasets from the two independent crosses sharing PERA as the gallstone susceptible parental strain based on a binary allelic model. Expression of candidate genes was determined by real-time PCR.

RESULTS: QTL mapping in the PERA x DBA/2 cross revealed one significant new {Lith} locus on chromosome 13 ({Lith15}) and two new suggestive QTL on Chr 1 and Chr 5. Furthermore additional QTL confirmed {Lith} loci from the former cross on Chr 2 ({Lith12}) Chr 6 ({Lith6}) and Chr 16 ({Lith14}). Our analysis of the combined crosses confirmed a shared QTL on Chr 17 ({Lith9}). In contrast no association was detected with {Lith7} that was

inherited from strain I/Ln in the former cross. We detected significantly higher mRNA expression of {Fxr} in strain I/Ln compared with strains PERA and DBA/2. Significantly higher mRNA expression of {Abcg5}/{Abcg8} in strain PERA compared with strains I/Ln and DBA/2 correlated positively with higher biliary cholesterol concentration.

CONCLUSION: Higher expression levels of {Abcg5/Abcg8} in strain PERA compared with I/Ln and DBA/2 further substantiate that these genes underlie the {Lith9} locus. Since no association was detected with {Lith7} we conclude that strains PERA and DBA/2 display genetic identity in the corresponding genomic region. Therefore identical expression levels of {Fxr} between these two strains but higher expression in I/Ln indicate that the {Fxr} allele from strain I/Ln underlies {Lith7}. This study underscores that dysregulated bile salt synthesis and polymorphisms of the canalicular cholesterol transporter are principle causes of cholesterol gallstone formation in inbred mice.

AAAT

Oral Presentation

Liver Disease - Basic science - Panorama Hall (Room 5)

Monday September 27 2004 11.00-12.30

Abstract: OP-G-12

0 Citation: Gut 2004; 53 (Suppl VI) A4

DEFICIENCY OF INDUCIBLE NITRIC OXIDE SYNTHASE EXACERBATES HEPATIC FIBROSIS IN MICE FED HIGH-FAT DIET

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INTRODUCTION: Although iNOS is known to be induced in liver of nonalcoholic steatohepatitis its role in the progression to fibrosis remains to be elucidated. Matrix metalloproteinases (MMPs) are central to fibrolysis and tissue remodeling through degradation of the main extracellular matrix components of liver fibrosis. We hypothesized that NO might participate in the process of liver fibrosis in steatohepatitis by directly modulating the expression of collagens and MMPs.

AIMS & METHODS: The aim of the present study is to examine the role of iNOS in the progression to fibrosis from steatohepatitis by comparing iNOS knockout (iNOS−/−) and wild-type (iNOS+/+) mice that were fed a high-fat diet starting from 8 weeks of age for 12 weeks. For the evaluation of fatty deposition the liver tissues were stained with Oil red O and counterstained with hematoxylin and eosin. The presence of collagen in the lesions was examined in Azan-stained. RT-PCR were performed to determine mRNA levels of iNOS alpha-smooth muscle actin and procollagen I. Gelatin zymography and in situ zymography were performed to examine protein expressions for MMPs.

RESULTS: Severe fatty metamorphosis developed in the liver tissues of iNOS+/+ and iNOS−/− mice to the same degree. According to both histopathological study and RT-PCR analysis fibrotic changes were marked in iNOS−/− mice but mild in iNOS+/+ mice. Gelatin zymography of liver homogenates showed that pro MMP-2 and pro MMP-9 proteins were induced in both iNOS+/+ mice but the degree of expression of both proenzymes was weaker in iNOS−/− mice than in iNOS+/+ mice. It is noteworthy that active forms of MMP-2 and MMP-9 were clearly present in the liver tissue of iNOS+/+ mice but only barely detectable in that of iNOS−/− mice. In situ zymography showed strong gelatinolytic activities in the liver tissue of iNOS+/+ mice but only spotty gelatinolytic activity in iNOS−/−mice.

CONCLUSION: We conclude that iNOS attenuates the progression of liver fibrosis during steatohepatitis in part by inducing MMP-2 and MMP-9 expression and augmenting their activity.

AAAU

Oral Presentation

Liver Disease - Basic science - Panorama Hall (Room 5)

Monday September 27 2004 11.00-12.30

Abstract: OP-G-13

0 Citation: Gut 2004; 53 (Suppl VI) A5

DIFFERENTIAL EXPRESSION OF TWO ISOFORMS OF THE CHEMOKINE RECEPTOR CXCR3 DETERMINES THE ULTIMATE EFFECT OF IP-10 ON THE SURVIVAL OF HUMAN HEPATIC STELLATE CELLS (HSC)

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INTRODUCTION: Activated human HSC express the chemokine receptor CXCR3 which binds IP-10 and induces cell migration. Recently an alternatively spliced isoform CXCR3-B has been described in microvascular endothelial cells. Unlike the classic isoform CXCR3-A CXCR3-B leads to growth inhibition and apoptosis and mediates angiostatic effects of IP-10.

AIMS & METHODS: Because the possible role of CXCR3-B expression in HSC is unknown we investigated the biologic significance of the IP-10/CXCR3 system in these cells considering the role of CXCR3-B and we established the signal transduction pathways associated with activation of the two receptor isoforms. Different lines of HSC were isolated from normal human liver tissue. Human embryonic kidney (HEK)-293 cells were transfected with expression vectors encoding for the two isoforms of the receptor under the control of a CMV promoter. Expression of CXCR3-A and CXCR3-B on HSC was assessed by Real Time PCR. Apoptosis of activated HSC was induced by Fas activation with or without cycloheximide and was evaluated by PARP cleavage and caspase 3 activation.

RESULTS: Activating anti-Fas antibody and/or cycloheximide induced HSC apoptosis which was inhibited by low concentrations of IP-10. However the inhibition of apoptosis by IP-10 was variable in different cell lines and tended to disappear after prolonged cell culture when a pro-apoptotic effect was actually observed. To test for this apparent paradox expression of CXCR3-A and CXCR3-B was evaluated in cells that did not show increased survival with IP-10. We observed that these cells expressed much higher levels of CXCR3-B than CXCR3-A thus

providing a mechanism for the reversal of the anti-apoptotic effects by IP-10. The signaling of HEK 293 transfected with the CXCR3-A isoform is similar to that of activated HSC after incubation of the cells with IP-10 we observed activation of Erk Akt and Src. On the other hand activation of CXCR3-B inhibited the phosphorylation of ERK and Akt induced by EGF but not EGF receptor phosphorylation. These data suggests a novel cross-talk mechanism between the CXCR3-B and growth factor receptors leading to the inhibition of ERK and Akt activation.

CONCLUSION: HSC may express both CXCR3 isoforms that mediate opposing effects of IP-10 on apoptosis. The ultimate biologic effect of autocrine IP-10 secretion depends on the relative expression of the two isoforms.

AAAV

Oral Presentation

Liver Disease - Basic science - Panorama Hall (Room 5)

Monday September 27 2004 11.00-12.30

Abstract: OP-G-14

0 Citation: Gut 2004; 53 (Suppl VI) A5

MECHANISM OF SUPPRESSION OF HUMAN CAR (NR113) GENE EXPRESSION BY INTERLEUKINE 1BETA AND LIPOPOLYSACCHARIDE: ROLE OF NFKB

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INTRODUCTION: The drug-metabolizing cytochrome P450 (CYP) enzymes are down-regulated during inflammation. This suppression can result in increased clinical toxicity of drugs. Conversely some drugs are converted to their pharmacologically active or toxicologically active metabolites by these enzymes and suppression of their metabolism can lead to a reduced therapeutic or toxic effect.

AIMS & METHODS: Our resarch has focused on the negative regulation of the orphan nuclear receptor CAR (NR1I3) by proinflammatory cytokines such as interleukin-1b (IL-1b) and lipopolysaccharide (LPS) in human hepatocytes. CAR is a key transactivator of CYP2B and CYP3A upon phenobarbital administration.

RESULTS: We found that IL-1b and LPS decrease CAR expression and suppress phenobarbital-mediated CYP2B6 and CYP3A4 induction in human hepatocytes. Moreover our data suggest that activation of nuclear factor-kB (NF-kB) is a critical event in LPS− or IL-1b-mediated inhibition of CAR expression through the repression of ligand-activated glucocorticoid receptor (GR) action. We observed that NFkB p65 interferes with the enhancer function of the distal glucocorticoid response element of the CAR promoter gene that we have identified recently. We demonstrated that: i) LPS IL-1b or p65RelA overexpression down-regulated GR activated CAR expression; ii) these suppressive effects could be blocked both by pyrrolidine dithiocarbamate which is known to inhibit NF-kB activation or by the overexpression of NF-kB repressor (SRIkBa). Finally using chromatin immunoprecipitation we demonstrated that GR agonist dexamethasone induces histone H4 acetylation at the proximal CAR promoter region whereas LPS and IL-1b inhibit this acetylation. These data suggests that GR/NF-kB interaction converges at the level of CAR transcription involving chromatin remodeling.

CONCLUSION: The results of this study may provide a mechanistic explanation for the long standing observation that sepsis-induced repression of CYP enzymes while inducing cholestasis and hyperbilirubinaemia.

AAAW

Oral Presentation

Liver Disease - Basic science - Panorama Hall (Room 5)

Monday September 27 2004 11.00-12.30

Abstract: OP-G-15

0 Citation: Gut 2004; 53 (Suppl VI) A5

NAFAMOSTAT MESILATE A SERINE PROTEASE INHIBITOR SUPPRESSES LIPOPOLYSACCARIDE-INDUCED LIVER INJURY BY DOWNREGULATING TLR-4

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INTRODUCTION: Bacterial lipopolysaccharide (LPS; endotoxin) an abundant and essential component of the outer membrane of Gram-negative bacteria provokes a generalized proinflammatory response in the infected host that sometimes leads to sepsis and multiple organ failure (MOF). The Toll-like receptor (TLR) family represents a set of essential surface molecules involved in recognition of microbe-derived products to activate host innate immunity.

TLR-4 acts as transmembrane receptors for LPS coordinately with CD14.

Nafamostat mesilate a serine protease inhibitor that is used for patients with pancreatitis or disseminated intravascular coagulopathy.

AIMS & METHODS: The present study aimed at investigating the influence of a serine protease inhibitor on LPS-induced liver injury by evaluating cytokine response to bacterial endotoxins.

Male Wistar rats were randomly divided into two groups. Group I received intra-peritoneal injection of phosphate-buffered saline (PBS) and after 30 minutes later received intra-portal LPS(500 mg/Kg) administration under ether anesthesia and Group II received intra-peritoneal injection of Nafamostat mesilate (2.5 mg/Kg) and after 30 minutes later intra-portal LPS administration under ether anesthesia designated as septic model. Blood samples were collected from the inferior vena cava and livers were removed and tissue samples were taken and snap-frozen in liquid nitrogen

AST ALT TNF-a IL-1b IL-6 IFN-g HGF(Hepatocyte growth factor) were measured by ELISA and TLR-4 and CD14 expression were examined by RT-PCR and immunohistochemistry

RESULTS: Serum AST and ALT levels were decreased in the Nafamostat mesilat treated rats than untreated rats.

Serum levels of TNF-a IL-1b IFN-g and HGF in the Nafamostat mesilate treated group were all decreased than the untreated group. IL-6 was not different in the both groups. TLR-4 and CD14 mRNA expression were decreased in the Nafamostat mesilata treated group and TLR-4 and CD14 protein expression were decreased in the Nafamostat mesilate trated group than the untreated group.

CONCLUSION: Nafamostat mesilate protected the liver from LPS expose by downregulating the TLR-4 and CD14 expression in the liver.

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AAAX

Oral Presentation

Liver Disease - Basic science - Panorama Hall (Room 5)

Monday September 27 2004 11.00-12.30

Abstract: OP-G-16

0 Citation: Gut 2004; 53 (Suppl VI) A5

INTRAPERITONEAL ADMINISTRATION OF HUMAN CORDONAL STEM CELL CAN CONTRIBUTE TO LIVER REGENERATION AFTER ACUTE HEPATIC DAMAGE IN NOT-MYELOABLATED RATS

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INTRODUCTION: Tissue homeostasis and turnover are guaranted by the stem proliferating reserve. Several studies performed with immunodeficient animals suggested that a particular degree of plasticity is shown by the haematopoietic stem cell (HSC) compartment that could be a source for liver regeneration (1-4).

AIMS & METHODS: We aimed to explore the hepatic differentiation potential of human HSC also in immunocompetent rats after a toxic liver damage.

Winstar rats were so sorted: Group A: liver damage (AA intraperitoneally ip); human HSC injection (ip) after 1 day and killing at 1 3 6 days after HSC injection. Group B: human HSC injection (ip) and killing at 1 3 6 days after. Group C: liver damage with Allyl Alcohol (AA) intraperitoneally (ip) injection and killing at 2 4 7 days after. Group D: sacrifice without any treatment. Livers spleens and bone marrows were analysed for human HSC detection using Flow Cytometry (FCM); livers were also tested with immunohistochemistry (IHC) to show the HSC transdifferentiation into hepatocytes.

RESULTS: FCM confirmed the presence of human HSC (groups B and A) and revealed their selective recruitment into the damaged livers (group A) in comparison with the controls (group B). IHC demonstrated the HSC capability to transdifferentiate into hepatic cells also in immunocompetent animals.

CONCLUSION: Our study demonstrated that HSC are able to contribute in liver regeneration after an acute toxic damage in not-myeloablated recipients opening doors to speculations about

their future applications for human liver diseases without the need of immunosuppressive pre-treatments.

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AAAY

Oral Presentation

Liver Disease - Basic science - Panorama Hall (Room 5)

Monday September 27 2004 11.00-12.30

Abstract: OP-G-17

0 Citation: Gut 2004; 53 (Suppl VI) A5

IN VITRO-PROPAGATED NORMAL HEPATOCYTES PROLONG THE SURVIVAL TIME OF RATS WITH ACUTE LIVER FAILURE

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INTRODUCTION: Orthotopic liver transplantation (OLT) is thought to be the most effective treatment for acute liver failure (ALF). However OLT is limited because of the difficulties to provide a suitable graft in emergency cases and the shortage of donor organs. Recently we demonstrated that rat or human hepatocytes can divide repeatedly if appropriate condition is provided. Our concept of hepatocyte transplantation is to proliferate normal hepatocytes without gene manipulation and to realize auto-or allotropic hepatocyte transplantation safely instead of the treatment of OLT.

AIMS & METHODS: The aim of this study was to evaluate the effect and its mechanism of intrasplenic transplantation of {in vitro}-propagated rat normal hepatocytes on elongation of survival time of rats with ALF. Dipetidylpeptidase IV negative (DPPIV-) Fischer 344 rats were induced for acute liver failure (ALF) by combining resection of two anterior liver lobes (68% of liver) with ligation of the right lobe (24% of liver) pedicle. Donor hepatocytes were isolated from DPPIV+ Fischer 344 rats and co-cultured with Swiss 3T3 cells resulting in proliferation about 3-fold for 11 days. Fifteen million of propagated hepatocytes (PH) were transplanted intrasplenically at 48 hrs before induction of ALF. Same number of isolated hepatocytes (IH) were also transplanted as positive control and cell free medium was injected as negative control.

RESULTS: Survival time of rats in PH group was longer than that in control group (65.4±b145.0 hors vs. 23.1±b15.8 hours;{P} <0.01) as well as that in IH group (70.0±b144.7 hours).

PH− and IH-transplantation improved blood parameters (NH_3 T.Bil. GOT and GPT) and decreased frequency of apoptosis and increased BrdU incorporation in hepatocytes of the remnant liver.

CONCLUSION: We concluded that the {in vitro}-propagated hepatocytes are useful as source of hepatocyte transplantation for patients with ALF and have a great potential in future clinical application.

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Oral Presentation

Liver Disease - Basic science - Panorama Hall (Room 5)

Monday September 27 2004 11.00-12.30

Abstract: OP-G-18

0 Citation: Gut 2004; 53 (Suppl VI) A6

THE EXPERIMENTAL STUDY OF HEPATIC INJURY DURING STOP-FLOW CHEMOTHERAPY IN PORCINE MODEL

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INTRODUCTION: Stop-flow chemotherapy is a newly developed regional chemotherapy procedure by means of blockading the blood supply of tumor bearing territory with inflated balloons and providing higher local concentration of chemotherapeutic medicines than intra-arterial and intravenous drugs injection. We have found a hepatic injury after stop-flow chemotherapy in animal model. But the hepatic pathophysiology upon such particular hypoxia/re-oxygenation hasn't been investigated till now.

AIMS & METHODS: To elucidate the potential mechanism of hepatic injury in abdominal stop-flow chemotherapy. The stop-flow chemotherapy was established in porcine model and eighteen pigs were randomized into 3 groups which were SF(only receiving stop-flow) group SFC (receiving stop-flow and chemotherapy) group and SHAM group respectively. The content of MDA activity of SOD and GSH-PX were measured to estimate the redox status after stop-flow procedure. The activation of NF-kappaB and STAT-3 was evaluated by EMSA and western blot. IkappaB-alpha and its phosphorylated form were determined by western blot and immunoprecipitation/western blot respectively. RT-PCR and ELISA were applied to investigate the change of TNF-alpha IL-1beta IL-8 Bak and Bcl-xL. The activity of Caspase-3 was also investigated. And the extent of hepatic injury was estimated with serum level of ALT AST and LDH.

RESULTS: There was not a substantial change in the level of MDA SOD and GSH-PX in liver at the early phase (<30min) after the stop-flow procedure in SF and SFC group when compared with SHAM group. NF-kappaB was activated and reached its highest level at 30min after the restoration of abdominal circulation accompanying with the phosphorylation and degradation of IkappaB-alpha and then decreased due to the reverse feedback regulation of NF-kappaB/IkappaB-alpha pathway in SF and SFC group meanwhile there was an increased activation of STAT-3 following the restoration of abdominal circulation. The mRNA of TNF-

alpha IL-1beta and IL-8 was elevated according to the activation of NF-kappaB ($P<0.05$) when compared with SHAM group. We also identified an increase of Bak Bcl-xL and Caspase-3 activity. There was a slight rise of MPO which in hepatic parenchyma after the restoration of abdominal circulation. The serum level of ALT AST and LDH declined after reaching their highest level at 24h after stop-flow procedure and fell back to pre-operative level in 7d.

CONCLUSION: The activation of NF-kappaB/IkappaB-alpha pathway was responsible for the hepatic influence after stop-flow procedure. Its reverse feedback regulation and the activation of STAT-3 limited the hepatic injury upon the hypoxia/re-oxygenation following this procedure.

AABA

Oral Presentation

Endoscopic approaches to micro-anatomy - Small Hall (Room 6)

Monday September 27 2004 11.00-12.30

Abstract: OP-E-19

0 Citation: Endoscopy 2004; 36 (Suppl I) A6

USEFULNESS OF VITAL DOUBLE DYE STAINING AND HIGH-MAGNIFICATION ENDOSCOPY FOR DETECTION OF SPECIALIZED COLUMNAR EPITHELIUM IN PATIENTS WITH REFLUX ESOPHAGITIS

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INTRODUCTION: Barrett's esophagus (BE) is associated with increased risk of malignancy. Specialized columnar epithelium (SCE) occurs in 10-15% of patients with chronic reflux esophagitis (RE). The use of techniques that can identify pathologic changes in distal part of the esophagus would be beneficial with respect to the diagnosis of BE.

AIMS & METHODS: The aim of this study was to compare the detection of SCE by using double staining chromoendoscopy versus random biopsies and to evaluate the usefulness of high-magnification endoscopy (HME) in diagnosis of esophageal pathology. 42 pts (28 M 14 F mean age 56) with RE were examined by conventional endoscopy with biopsy between January 2003 and May 2004. Then all of them during 4-8 weeks period underwent endoscopy using double staining method with directed biopsies. We used chromoendoscopy with Lugol for dyeing of squamous epithelium and methylene blue (MB) for dyeing of SCE. In 20 pts we performed HME (Olympus GIF Q160Z) with 115x magnification. Biopsy specimens were stained with H&E and alcian blue.

RESULTS: After Lugol normal squamous epithelium is stained dark brown; gastric fundic type junctional type epithelium in distal esophagus erosions dysplasia produces unstained areas. MB was used after Lugol for selective staining of SCE in unstained areas without erosions or ulcers. SCE was diagnosed in 3 pts (7%) after conventional endoscopy with 4-quadrant random biopsies obtained every 2 cm of distal esophagus and in 6 pts (14%) after double staining with directed biopsies (1 long-segment BE 5 shot-segment BE) and confirmed by histology. HME was performed before the MB staining as well as after in 6 pts with BE and in 14 pts with RE. We evaluated intrapapillary capillary loop (IPCL) of esophageal mucosa[1]. In all pts with RE and BE we diagnosed dilatation and elongation of IPCL (type 2). Gastric fundic type or junctional

type epithelium had a spot or short-linear pit pattern. SCE had a regular villous pattern. In 1 case we diagnosed disturbed villous pattern (histology showed severe dysplasia). HME helped to distinguish pit pattern changes between erosions and SCE which were both dyed by MB.

CONCLUSION: Method of vital double dye staining with HME is very useful for diagnosis of minute mucosal changes in distal part of the esophagus in pts with RE. MB directed biopsies led to increase the detection of SCE compared to random biopsies. Magnifying observation of BE according to the mucosal pattern changes would predict SCE but it needs further study.

Reference: H. Inoue et al. High-magnification endoscopic diagnosis of the superficial esophageal cancer. Digestive endoscopy 2000 Vol12:32-35.

AABB

Oral Presentation

Endoscopic approaches to micro-anatomy - Small Hall (Room 6)

Monday September 27 2004 11.00-12.30

Abstract: OP-E-20

0 Citation: Endoscopy 2004; 36 (Suppl I) A6

ENDOSCOPIC AND MAGNIFYING ENDOSCOPIC FINDING OF NORMAL STOMACH WITHOUT H. PYLORI INFECTION AND ADENOCARCINOMA ARISING FROM H. PYLORI-FREE NORMAL STOMACH

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INTRODUCTION: Endoscopic feature of normal stomach without H. pylori infection is the arrangement of minute points visible on the corpus [1]. These points were clarified by magnifying endoscopy as collecting venules this finding was termed ``regular arrangement of collecting venules'' (RAC) [1 2].

AIMS & METHODS: The aim was clarifying accurate of the RAC as H. pylori-negative normal stomach and adenocarcinoma arising from normal stomach without H. pylori infection.

The study group consisted of 557 patients who were subjected to endoscopy and checked for H. pylori by histology and culture. The RAC in each patient was assessed. Magnifying endoscopy in 301 patients was used.

RESULTS: 158 patients had H. pylori-negative normal stomach. 389 patients had H. pylori-induced gastritis. In 10 patients H. pylori was not detected but gastritis was present. Of the 158 H. pylori-negative normal patients 151 showed RAC. As a determinant of the normal stomach without H. pylori infection the presence of RAC had 93.8% sensitivity and 96.2% specificity. Magnified view of RAC showed collecting venules with true capillaries forming a network and gastric pits with pinhole appearance (type Z-0) [2]. Magnified view of corpus on H. pylori-induced gastritis showed three types: irregular true capillaries but no collecting venules (Z-1) white pits and sulci with neither collecting venules nor true capillaries (Z-2) and dilated pits with surrounding redness (Z-3) [2]. In this study we found two cardiac cancers and three adenocarcinomas arising from short-segment Barrett's esophagus. The stomachs in all five cases were diagnosis as RAC-positive during endoscopic examination. Later all five cases were ascertained to be H. pylori-negative normal stomach by biopsy and serological testing. We also found 19 cases of non-cardiac cancer (diffuse type). In these cases the stomachs were diagnosed

as RAC negative during endoscopic examination. All 19 cases were confirmed to have H. pylori-induced gastritis by biopsy.

CONCLUSION: RAC-diagnosis is useful because we were able to diagnose H. pylori infection during endoscopic examination before we aware of the results of the biopsy. Adenocarcinoma arising from esophago-gastric junction was thought to have no connection with H. pylori infection. RAC-diagnosis contribute to endoscopist in studying the relationship between various esophago-gastric disease and H. pylori infection.

Reference: Yagi K et al. Characteristic endoscopic and magnified endoscopic findings in the normal stomach Helicobacter pylori infection. J Gastroenterol Hepatol 2002;17:39-45.

Yagi K et al. Comparison between magnifying endoscopy and histological culture and urease test findings from the gastric mucosa of the corpus. Endoscopy 2002;34:376-381

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Oral Presentation

Endoscopic approaches to micro-anatomy - Small Hall (Room 6)

Monday September 27 2004 11.00-12.30

Abstract: OP-E-21

0 Citation: Endoscopy 2004; 36 (Suppl I) A6

NOVEL ZOOM-ENDOSCOPY TECHNIQUE FOR VISUALIZING THE MUCOSAL MICROVASCULAR ARCHITECTURE IS USEFUL FOR MAKING A CORRECT DIAGNOSIS OF GASTRIC REDDENED FLAT MUCOSAL LESIONS (GASTRITIS VS. GASTRIC CANCER)

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INTRODUCTION: It is often difficult using standard endoscopy to make an endoscopic diagnosis of the flat type of early gastric cancer that mimics gastritis. We previously reported the magnified endoscopic findings of the microvascular architecture of differentiated type of flat reddened gastric carcinoma (1).

AIMS & METHODS: The aim of this study was to investigate the diagnostic accuracy of these magnified endoscopic findings for differentiating between reddened mucosa due to gastritis and flat reddened gastric cancer prospectively. Methods: 485 cases were included in this study. The patients received upper gastrointestinal endoscopic examination for the screening of gastric cancer by zoom endoscope GIF-Q240Z (Olympus Tokyo Japan). If a flat reddened lesion was detected by non-magnified observation the lesion was subsequently magnified by a zooming attachment. Immediately after the examination the following findings which have been reported to be characteristic of carcinoma were recorded. (1) Presence of a demarcation line between the reddened lesion and the surrounding mucosa (2) Disappearance of a regular subepithelial capillary network pattern of the same shape as that within the surrounding mucosa and (3) Proliferation of microvessels irregular in both shape and distribution (irregular microvascular pattern). According to the pathological diagnosis the flat reddened lesions were divided into two groups i.e. gastritis and carcinoma groups. The incidence and 95% confidence intervals (CI) of these findings were calculated for each of the respective groups.

RESULTS: 187 flat reddened lesions from 187 cases were detected. Pathologically 136 lesions showed only gastritis while 51 lesions were diagnosed as differentiated carcinoma. The incidence (95% CI) of the magnified endoscopic findings in gastritis vs. carcinoma was (1)

24.3% (17.1-31.5%) vs. 94.1% (87.6-100%) (2) 21.3% (14.4-28.2%) vs. 100% and (3) 0.7% (0-2.1%) vs. 98.0% (94.2-101.8%) respectively. As for the differential diagnosis of carcinoma from gastritis the sensitivity and the specificity of the irregular microvascular pattern were 98.0% and 99.3% respectively.

CONCLUSION: An irregular microvascular pattern visible by magnified endoscopy can be a very useful marker for differentiating between gastritis and carcinoma.

Reference: Yao K et al. Novel magnified endoscopic findings of microvascular architecture in intramucosal gastric cancer. Gastrointest Endosc 2002; 56: 279-84.

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Oral Presentation

Endoscopic approaches to micro-anatomy - Small Hall (Room 6)

Monday September 27 2004 11.00-12.30

Abstract: OP-E-22

0 Citation: Endoscopy 2004; 36 (Suppl I) A6

NOVEL ZOOM-ENDOSCOPY TECHNIQUE FOR VISUALIZING THE MICROVASCULAR ARCHITECTURE OF EARLY GASTRIC CANCER ENABLES THE PRECISE MARGIN OF THE CANCER TO BE DETERMINED THEREBY ALLOWING SUCCESSFUL RESECTION BY THE ENDOSCOPIC SUBMUCOSAL DISSECTION METHOD

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INTRODUCTION: The endoscopic submucosal dissection (ESD) method enables the endoscopist to resect a large early gastric cancer en bloc. In order to carry out successful resection however it is essential to determine the horizontal margin of the cancer. To date no specific method has been established for determining the precise margin by endoscopic findings alone. Recently we reported novel magnified endoscopic findings characteristic for early gastric cancer (1). With magnification early gastric cancers constantly demonstrated a clear demarcation line between the irregular microvascular pattern in the cancerous mucosa and the regular subepithelial capillary network pattern in the noncancerous mucosa even when the cancer showed an unclear margin by non-magnified observation.

AIMS & METHODS: We prospectively investigated whether these magnified endoscopic findings are useful for a preoperative diagnosis of the horizontal margin of the cancer. 47 early gastric flat cancers of differentiated-type were included in the study. The median diameter of the cancer was 15 mm (range 3-50 mm). All the cancers were examined by the zoom upper gastrointestinal endoscope GIF-Q240Z (Olympus Tokyo). According to subsequent observation following the non-magnified observation all the demarcation lines between the cancerous and the noncancerous mucosa had been identified. Then several markings were made on the mucosa a few millimeters outside the demarcation lines by electrocoagulation. The cancerous mucosa together with all the markings was subsequently resected by the ESD method. According to the histrogical findings of the resected specimen we investigated whether or not the horizontal cut ends were free from cancerous tissue and whether the markings had been correctly placed outside the cancerous mucosa.

RESULTS: The median diameter of the resected specimens was 35 mm (range 16-90 mm). 43 cancers were resected en bloc while 3 cancer were resected in 2 to 8 pieces. Only one of the horizontal margins of one specimen showed positive findings for cancerous tissue. All the margins of the other 46 lesions demonstrated negative findings for cancerous tissue and all the markings were located outside the cancerous tissue by histopathological investigation.

CONCLUSION: The novel zoom endoscopy technique which can visualize differences in the microvascular architecture could be useful for determining the horizontal extent of early gastric carcinomas which can then be resected by the ESD method.

Reference: Yao K et al. Novel magnified endoscopic findings of microvascular architecture in intramucosal gastric cancer. Gastrointest Endosc 2002; 56: 279-84.

AABE

Oral Presentation

Endoscopic approaches to micro-anatomy - Small Hall (Room 6)

Monday September 27 2004 11.00-12.30

Abstract: OP-E-23

0 Citation: Endoscopy 2004; 36 (Suppl I) A7

GASTRIC CARDIA: EXPLORATION OF CARDIAL MUCOSA WITH NBI SYSTEM

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INTRODUCTION: The gastric cardia is a small zone that is normally located just below the squamo-columnar junction (Z-line). Recent studies on pathogenetic factors for inflammation in cardial mucosa (carditis) and on the significance of intestinal metaplasia in gastric cardia have yielded contradictory results perhaps because of the fundamental differences in the techniques used for identifying and sampling the cardial mucosa.

AIMS & METHODS: To endoscopically identify cardial mucosa with the help of the NBI (Narrow Band Imaging) system. The gastric cardia was examined by using NBI system (Olympus) a magnifying endoscope (GIF-Q240Z Olympus) and a 3% solution of acetic acid. By using special optical filters the NBI system changes the spectrum of incident light and utilizes the superficial absorption and photon reflection of the short wavelength blue range (400-430 nm). By changing the spectral characteristics of the observational light NBI allows for improving the endoscopic image quality related to mucosal patterns and capillary arrangement.

RESULTS: From November 2002 to April 2004 we examined 125 patients with reflux symptoms. Patients with a histology of intestinal metaplasia were excluded. Using NBI with magnification and acetic acid chromoscopy we evaluated the esophago-gastric junction region and were able to identify typical surface patterns of three types of mucosa that correlate perfectly with the histology results:

-pattern with small round pits which are regular in shape and arrangement no wide grooves are present corresponds to fundic mucosa;

-pattern with pits that are circular or oval and are regular in shape and arrangement no wide grooves are present corresponds to cardial or mixed (fundic and cardial) mucosa;

-pattern with convoluted shape like cerebriform appearance and with thin bending grooves may represent inflammation of pure cardial mucosa.

Cardial mucosa was usually present as microscopic zone (3-5 mm in length) just below Z-line. The pure cardial mucosa could be absent in the entire circumference of the esophagogastric junction and moreover in approximately 50% of the patients pure cardial mucosa was completely absent.

CONCLUSION: Pure cardial mucosa at the junction is frequently absent has considerable individual variation is very small in extent when present is commonly absent from some part of the circumference of the junction. These characteristics of pure cardial mucosa should be taken into consideration for the developing practical guidelines for biopsy protocols to be used in future studies. The mucosal pattern with convoluted shape like cerebriform appearance and with thin bending grooves may represent an early marker of gastroesophageal reflux.

AABF

Oral Presentation

Endoscopic approaches to micro-anatomy - Small Hall (Room 6)

Monday September 27 2004 11.00-12.30

Abstract: OP-E-24

0 Citation: Endoscopy 2004; 36 (Suppl I) A7

OBSERVATION OF BARRETT'S MUCOSA BY MAGNIFYING CHROMOENDOSCOPY AND NARROW BAND IMAGING ENDOSCOPY

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INTRODUCTION: Specialized columnar epithelium (SCE) in Barrett's esophagus has been detected by random or four quadrant biopsy using conventional endoscopy; however little is known about the relation among fine mucosal structure of Barrett's mucosa histological features mucin phenotype and cellular proliferation.

AIMS & METHODS: The fine mucosal pattern (pit pattern) of 70 regions in Barrett's mucosa was recorded and compared with methylene blue staining using magnifying endoscopy. Histological mucin immunohistologic and cell proliferation analyses of biopsy specimens were performed in relation to the pit patterns obtained by magnifying endoscopy. On the other hand a newly developed endoscope lighting system called Narrow Band Imaging (NBI) is a system that emphasizes certain histological features such as capillary and surface mucosal structure. Magnifying endoscopy was performed by using both a conventional system and an NBI system. All images were recorded by both video and a digital still image filing system. The differences of images among conventional dye spraying and NBI were evaluated by experienced endoscopists. The quality of images for visualization of squamocolumnar junction squamous island capillary vessels and pit patterns were judged to be optimal (score of 4) diagnostic (3) sub optimal (2) or non-diagnostic (1).

RESULTS: Pit patterns were classified into five categories. Tubular or villous pit patterns were not only characteristics of both SCE and methylene blue absorption but also possessed intestinal mucin phenotype whose Ki-labeling index was high while other pit patterns dot or straight pattern did not have SCE and were categorized into gastric phenotype mucosa. Long oval pit pattern had an intermediate phenotype between these two groups. In contrast to conventional endoscopy NBI endoscopy captured the optimal view of Barrett's epithelium. The relationship between the endoscopic and histopathologic diagnosis was more accurate by NBI endoscopy than conventional magnifying endoscopy.

CONCLUSION: Classification of superficial mucosal appearance obtained by magnifying endoscopy reflects not only histological features but also cellular functions of Barrett's mucosa.

Magnifying endoscopy by NBI is more useful than conventional magnifying endoscopy for diagnosis of BE.

AABG

Oral Presentation

Endoscopic approaches to micro-anatomy - Small Hall (Room 6)

Monday September 27 2004 11.00-12.30

Abstract: OP-G-25

0 Citation: Gut 2004; 53 (Suppl VI) A7

NBI ENABLES ACCURATE ENDOSCOPIC DIAGNOSIS OF EARLY GASTRIC CANCER

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INTRODUCTION: The electronic endoscope is based on the ``Frame Sequential Image Pick-up'' method. The lighting unit is composed of a xenon lamp and a rotating disk with 3 optical filters. The rotating disk and the monochrome CCD are synchronized and sequentially 3 band images are generated. From these 3 band images one color image is synthesized by the video processor. Among these elements the spectrum features of RGB filters most strongly influence the information of the images. NBI is the technology based on the optimization of such spectrum features of the optical filter. We utilized the wave-length dependence of the light penetration depth into the tissue in designing the spectral transmittance of RGB filters for NBI. The gastric mucosa is the turbid medium in which the light propagates diffusely. The main absorber of light is hemoglobin and the scattering of the light depends on the cell structure. Therefore the light penetration depth into the tissue has also the wave-length dependence. For example the shorter wave-length light (blue light) can propagate to the shallow region of the mucosa. While the longer wave-length light (red light) can propagate more deeply into the tissue.

AIMS & METHODS: We observed 66 early gastric cancers using the NBI system with or without magnifying endoscope.

RESULTS: Using NBI with magnifying endoscope the surface capillaries of the early gastric cancer showed distinct abnormal patterns. After the observation partial gastrectomy or endoscopic mucosal resection (EMR) was performed for all the lesions for histological evaluation. The gastric cancer showed several different abnormal microvascular patterns according to the histopathological types i.e. well moderately or poorly differentiated adenocarcinoma. Moreover we could correctly determine the margin of the cancer in 62/66 (92%) of the lesions based on these microvascular patterns.

CONCLUSION: The NBI system with magnifying endoscope was useful for the accurate histopathological diagnosis and for determining the margin of early gastric cancer.

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Oral Presentation

Endoscopic approaches to micro-anatomy - Small Hall (Room 6)

Monday September 27 2004 11.00-12.30

Abstract: OP-E-26

0 Citation: Endoscopy 2004; 36 (Suppl I) A7

VIDEO AUTOFLUORESCENCE IMAGING (AFI) FOLLOWED BY NARROW BAND IMAGING (NBI) FOR DETECTION OF HIGH GRADE DYSPLASIA (HGD) AND EARLY CANCER (EC) IN BARRETT'S ESOPHAGUS (BE)

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INTRODUCTION: AFI is a novel endoscopic imaging technique that may improve the detection of HGD/EC in BE. However AFI is associated with a high false positive rate. NBI another new imaging technique improves the detection of mucosal and vascular patterns in BE which may correlate with histology. The combination of AFI and NBI may reduce the false positive rate and therefore increase the positive predictive value for HGD/EC.

AIMS & METHODS: The aim of this study was to investigate the feasibility of the combination of AFI-NBI for improving the positive predictive value for HGD/EC in BE. 14 patients with BE (13 work-up for HGD/EC 1 follow-up after endoscopic therapy; mean length BE 5 cm) were investigated with 2 prototype imaging systems: 1) AFI (Olympus Tokyo Japan) which has a sequential RGB light source and a high-resolution video-endoscope (HRE) with separate CCD's for white light endoscopy (WLE) and AFI; 2) NBI (Olympus Tokyo Japan) which has a sequential RGB light source equipped with conventional RGB rotary filters (for WLE) and a separate set of rotary filters with narrowed RGB band-pass ranges and increased contribution of blue light illumination (for NBI). A HRE with optical zoom (x 115) was used during NBI.

Patients were first examined with the AFI system: the BE was screened with WLE and all visible lesions were recorded followed by inspection with the AFI mode for additional abnormalities. Non-dysplastic BE appeared green on AFI while suspicious areas were found to have a blue to violet color. Subsequently upper endoscopy was performed with the NBI system for detection of the mucosal and vascular patterns of all lesions detected during AFI. Irregular mucosal and vascular patterns as well as abnormal blood vessels were considered suspicious while areas with regular patterns were regarded as not suspicious. All detected lesions were sampled for histopathological correlation.

RESULTS: From a total of 27 lesions with HGD/EC 16 were identified with WLE (sensitivity 59%) and 26 with AFI (sensitivity 96%). In total 34 suspicious lesions were detected with AFI: 26 contained HGD/EC (PPV 76%) and 8 were false positive (23%). After NBI no suspicious patterns were found in 7 of the 8 false positive lesions. Therefore the false positive rate was reduced to 4% and the PPV increased to 96%.

CONCLUSION: This uncontrolled study in a high-risk population of BE patients suggests that AFI can serve as a ``red flag'' technique to detect suspicious lesions and NBI can be applied to verify the presence of suspicious surface patterns. The combination of these 2 novel imaging techniques may increase the detection of HGD/EC in BE while reducing the false positive rate.

AABI

Oral Presentation

Endoscopic approaches to micro-anatomy - Small Hall (Room 6)

Monday September 27 2004 11.00-12.30

Abstract: OP-E-27

0 Citation: Endoscopy 2004; 36 (Suppl I) A7

VIRTUAL HISTOLOGY OF COLORECTAL LESIONS USING ENDO-CYTOSCOPY SYSTEM

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INTRODUCTION: We developed Endo-Cytoscopy (E-C) a novel `ultra-high' magnification endoscopy which enables cellular level microscopic observation and can be applied clinically. Reports on clinical application of E-C were made by Ooue (for colorectal cancer) Kumagai (for esophageal cancer) and Inoue (for esophageal and gastric cancer) at the same time in a symposium during DDW Japan at Fukuoka October 2003.

AIMS & METHODS: The aim of this study is to clarify the usefulness of E-C in the diagnosis of colorectal lesions. Endo-Cytoscopy with outside diameter of 3.4mm and full length of 250cm is a soft catheter-type endoscope which utilizes magnifying lens system for magnification. The Prototype I has magnifying capacity of 450 times and the Prototype II has that of 1125 times. The study materials consisted of 75 colorectal lesions. After spraying of 1% Methylene Blue dye the instrument is passed through the working channel of colonoscope (CF-Q240AI or CF-XT240I). Then real-time in vivo images of the lesions were obtained. All of 75 lesions were resected endoscopically or surgically after the observation. Diagnosis with E-C alone was attempted by a pathologist who was blinded to the pathological diagnosis. Then the E-C images for each lesion were compared with hematoxylin-eosin stained histopathological horizontal cross-sections.

RESULTS: It was possible to distinguish neoplastic lesions from non-neoplastic. And it was also possible to distinguish highly dysplastic adenomas from those with low-grade dysplasia. In adenocarcinomas the nuclei were enlarged and dense in chromatin but the structural atypia was so severe that gland formation was hardly recognized.

CONCLUSION: Ultra-high magnifying endoscopy E-C provides real-time histological images in vivo that correspond well with those of hematoxylin-eosin stained microscopic images. In other words it can be said that virtual histology has come true.

AABJ

Oral Presentation

Experimental pancreatitis - Meeting Hall 4 (Room 7)

Monday September 27 2004 11.00-12.30

Abstract: OP-G-28

0 Citation: Gut 2004; 53 (Suppl VI) A8

INDUCTION OF CASPASE-3-ACTIVITY IN PANCREATIC ACINAR CELLS AR4-2J BY TRANSFECTION WITH R122H TRYPSINOGEN AND ACTIVE TRYPSIN

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INTRODUCTION: The most frequent mutation associated to chronic hereditary pancreatitis is the R122H variant of cationic trypsinogen. According to biochemical data obtained from recombinant enzyme expressed in E. coli the R122H trypsinogen leads to a stabilisation of trypsin. Aim of our study was to investigate the effect of this mutation compared to wildtype trypsinogen in pancreatic acinar cells using the cell line AR4-2J as a model.

AIMS & METHODS: To obtain an expression vector for human cationic trypsinogen the cDNA is subcloned in pcDNA3 (pTry). The mutation R122H (pR122H) was introduced by site directed mutagenesis. We obtained the expression vector for intracellular active trypsin by subcloning the cDNA that codes for trypsin (without coding region for trypsin activating peptide) into pcDNA3 downstream of an unrelated signal peptide. Experiments were performed in AR4-2J or HeLa cells. Western blot and immunoprecipitation were used to verify protein expression. Activity of trypsin was measured fluorometrically after transfection in HeLa cells using a rhodamine coupled trypsin substrate. As marker for apoptosis we monitored the activity of caspase-3 in AR4-2J cells by cotransfection with the pCaspase-3-Sensor vector (pCas-3-S). It codes for a fusion protein of the enhanced yellow fluorescent protein (EYFP). A caspase-3 cleavage site followed by a dominant nuclear export signal (NES) is fused to the EYFP at the N-terminal end. C-terminal a nuclear localisation signal is placed. If caspase-3 is activated at the onset of the apoptotic process NES is cut of the fusion protein at the caspase-3 cleavage site. The remaining NLS then localises the EYFP fusion protein to the nucleus. AR4-2J cells were cotransfected with pCas-3 and the different expression vectors. With fluorescence microscopy apoptotic cells (nuclear staining) could be distinguished from non-apoptotic cells (cytoplasmatic staining) and quantified. The trypsin inhibitor Pefabloc and the caspase-3 inhibitor were added at different experiments.

RESULTS: pActTry showed a high trypsin activity compared to pTry and this activity could be blocked dose dependently by the trypsin inhibitor Pefabloc. Transfection of AR4-2J cells with pActTry or pR122H led to higher Caspase-3 activity than pTry. The higher Caspase-3 activity of both pActTry and pR122H could also be inhibited dose dependantly by Pefabloc. When induced by Staurosporine Caspase-3 activity could not be blocked. This shows the specifity of the inhibitor to trypsin.

CONCLUSION: Apoptosis is induced by expression of intracellular active trypsin and the R122H mutant of trypsinogen in AR4-2J cells. This effect could be inhibited specifically and dose dependantly by a trypsin inhibitor. Expression of R122H trypsinogen appears to induce apoptosis because of enhanced trypsin activity in AR4-2J cells.

AABK

Oral Presentation

Experimental pancreatitis - Meeting Hall 4 (Room 7)

Monday September 27 2004 11.00-12.30

Abstract: OP-G-29

0 Citation: Gut 2004; 53 (Suppl VI) A8

PROTEASE-ACTIVATED RECEPTOR-2-MEDIATED PROLIFERATION AND COLLAGEN PRODUCTION OF PANCREATIC STELLATE CELLS

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INTRODUCTION: In response to pancreatic injury or inflammation pancreatic stellate cells (PSCs) are transformed (\activated\) from their quiescent phenotype into highly proliferative myofibroblast-like cells which express the cytoskeletal protein alpha-smooth muscle actin and produce extracellular matrix components. Activated PSCs are implicated in the pathogenesis of pancreatic inflammation and fibrosis. Protease-activated receptor-2 (PAR-2) is a G protein-coupled receptor for trypsin and mast cell tryptase. Trypsin and tryptase cleave within the extracellular N-terminus of PAR-2 at SKGRA'SLIGRL yielding a tethered ligand (SLIGRL for rat PAR-2) that binds to the second extracellular loop activating the receptor. PAR-2 is widely expressed in human tissues with especially high levels in the pancreas liver kidney small intestine and colon. High expression of PAR-2 in the pancreas is interesting because trypsin is prematurely autoactivated within the inflamed pancreas and is believed to contribute to the development of pancreatitis.

AIMS & METHODS: This study aimed to clarify the role of PAR-2 in the activation of PSCs. PSCs were isolated from rat pancreas tissue. Expression of PAR-2 was examined by Western blotting. Trypsin activating peptide (SLIGRL-NH2 corresponding to the PAR-2 tethered ligand) and tryptase were tested for their ability to affect proliferation monocyte chemoattractant protein-1 cytokine-induced neutrophil chemoattractant-1 and collagen production in culture-activated PSCs. Activation of transcription factors was examined by electrophoretic mobility shift assay. Activation of mitogen-activated protein (MAP) kinases was assessed by Western blotting using anti-phosphospecific antibodies. The effect of PAR-2 agonists on the activation of freshly isolated PSCs in culture was also examined.

RESULTS: PAR-2 expression was observed in culture-activated PSCs whereas it was almost undetectable in freshly isolated PSCs. PAR-2 agonists activated activator protein-1 and MAP kinases (extracellular-signal regulated kinase c-Jun N-terminal kinase and p38 MAP kinase) but not nuclear factor kB. PAR-2 agonists induced proliferation of PSCs through the activation of

extracellular-signal regulated kinase. PAR-2 agonists increased collagen synthesis through the activation of c-Jun N-terminal kinase and p38 MAP kinase. PAR-2 agonists did not induce the production of monocyte chemoattractant protein-1 and cytokine-induced neutrophil chemoattractant-1 or initiate the transformation of freshly isolated PSCs in culture.

CONCLUSION: Our results suggest a role of PAR-2 in the development of pancreatic fibrosis through the increased proliferation and collagen production.

AABL

Oral Presentation

Experimental pancreatitis - Meeting Hall 4 (Room 7)

Monday September 27 2004 11.00-12.30

Abstract: OP-G-30

0 Citation: Gut 2004; 53 (Suppl VI) A8

MYELIN BASIC PROTEIN IN CEREBROSPINAL FLUID AND SERUM OF RATS WITH SEVERE ACUTE PANCREATITIS

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INTRODUCTION: pancreatic encephalopathy (PE) has not been completely elucidated. Most reports deal with the clinical characteristics of PE and discuss pathological findings and hypotheses. Histologicalal examination of the cerebral tissues in clinical cases and experimental models revealed diffuse demyelinization. However the myelin basic protein (MBP) level in cerebrospinal fluid (CSF) and serum of rat with severe acute pancreatitis (SAP) has not yet been well documented.

AIMS & METHODS: To investigate the relevance of CSF and serum MBP level of rat with SAP a serial analysis was performed. The model of SAP was induced in Sprague-Dawley rat edema pancreatitis (EP) and sham-operated rats served as controls. Cannulation of the cisterna magna were performed to obtain CSF sample. CSF and blood samples were obtained at sequential time points (3 6 9 12 24h) after model induced and were analyzed for MBP concentration using a sensitive enzyme-linked immunosorbent assay kit. Myelin sheaths of brain were analysed by electron microscope.

RESULTS: The kinetic CSF MBP concentration of SAP rat showed a rapid onset at 3h and remained high level at 6 9h showing significant differences comparing with EP or sham-operated group then followed by a slow decline at 12h (Table 1). Furthermore the concentrations of serum MBP between SAP and EP or sham-operated group did not show any significant differences remaining at very low levels. Under electron microscope ranish of structure of myelin sheaths diffuse demyelination and degeneration were observed in the SAP group.

Table 1. CSF MBP concentrations in SAP EP and sham-operation

MBP (ng/ml) 3h 6h 9h 12h 24h SAP (n=30) 20.5±3.3** 15.5±2.1* 16.2±3.6* 10.6±2.1 12.1±2.5 EP (n=30) 9.3±2.1 8.5±1.3 7.3±1.1 7.2±1.5 9.5±1.2 Sham-operation (n=30) 7.3±0.6 8.4±1.6 7.8±1.4 7.4±1.5 7.9±1.0

Values are mean±SEM. n = number of rats. One-way ANOVA followed by Tukey's test

CONCLUSION: The results support that the CSF MBP assay should serve as an index for destruction of nervous tissue during SAP and form a basis for the understanding of its kinetics which is important for the use in clinical practice. Interestingly the presence of MBP in the serum is not necessarily correlated with the highest level of CSF MBP.

AABM

Oral Presentation

Experimental pancreatitis - Meeting Hall 4 (Room 7)

Monday September 27 2004 11.00-12.30

Abstract: OP-G-31

0 Citation: Gut 2004; 53 (Suppl VI) A8

GREEN TEA CATECHIN INHIBITS ETHANOL-INDUCED RAT PANCREATIC STELLATE CELL ACTIVATION THROUGH ANTI-OXIDATIVE EFFECT

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INTRODUCTION: Pancreatic fibrosis is a key histopathological feature of chronic pancreatitis and of pancreatic cancer. Therefore the pathogenesis of pancreatic fibrosis has attracted great attention in recent years. Alcohol is now accepted as a major cause of chronic pancreatitis and now we know that pancreatic stellate cells (PSCs) play a central role in pancreatic fibrogenesis. Recently it has been reported that ethanol induced PSC activation increase of alpha-SMA expression and of type I collagen synthesis through the oxidative stress. Many reports show that major green tea extract catechins have potent anti-oxidative and radical scavenging effects.

AIMS & METHODS: To determine whether catechin blocks PSC activation induced by ethanol. PSCs were isolated from the pancreata of male Wistar rats by the Nycodenz solution. Cultured rat PSCs were incubated with 50 mM ethanol in the presence or absence of 5 25 or 50 microM (−)-epigallocatechin-3-gallate (EGCG). We assessed the effects of EGCG on (i) alpha-SMA expression: Western blot analysis and immunohistochemistry (ii) collagen synthesis and secretion: procollagen I alpha 2 mRNA expression by Real-time PCR and Sircol collagen assay (iii) cytokine synthesis: TGF-beta 1 mRNA expression by Real-time PCR (iv) DNA synthesis and cell proliferation: BrdU incorporation and cell proliferation assay and (v) oxidative stress: Mn-SOD and Cu/Zn-SOD mRNA expression by Real-time PCR.

RESULTS: In the presence of ethanol PSCs showed strong alpha-SMA immunofluorescence in the cell cytoplasm. On the other hand ethanol significantly increased alpha-SMA protein expression collagen synthesis and secretion cytokine synthesis. EGCG significantly inhibited ethanol-induced these expression in a dose-dependent manner. EGCG also significantly suppressed BrdU incorporation and cell proliferation in a dose-dependent manner. Ethanol significantly increased both Mn-SOD and Cu/Zn-SOD mRNA expression. EGCG significantly inhibited ethanol-induced both SODs expression.

CONCLUSION: These results indicate that green tea may be useful as a chemopreventive and chemotherapeutic agent against pancreatic fibrosis through anti-oxidative effect.

AABN

Oral Presentation

Experimental pancreatitis - Meeting Hall 4 (Room 7)

Monday September 27 2004 11.00-12.30

Abstract: OP-G-32

0 Citation: Gut 2004; 53 (Suppl VI) A9

IMMORTALISED HUMAN PANCREATIC STELLATE CELLS RETAIN THEIR CHRACTERISTIC PHENOTYPE

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INTRODUCTION: Progressive fibrosis is a characteristic feature of chronic pancreatitis of various etiologies as well as of pancreatic cancer. Until now the molecular mechanisms and cell-cell interactions leading to pancreatic fibrosis were largely unknown. Pancreatic stellate cells (PSCs) seem to be responsible for the development of pancreatic fibrosis. Because of the finite life span of these cells different cell preparations have to be used complicating the comparison of results when the mechanisms of fibrosis are analysed. To overcome this obstacle we tried to establish an immortal human pancreatic stellate cell line.

AIMS & METHODS: Cells growing out from small pancreatic tissue clumps obtained from chronic pancreatitis material were immortalised with SV40 large T antigen and the catalytic subunit of the human telomerase (hTERT). The expression of PSC markers epithelial and ductal markers was analysed by immunocytochemistry Western Blot and RT-PCR. The influence of TGFb1 on growth characteristics of the cells and on the expression pattern of genes implicated in pancreatic fibrosis was analyzed using the tetrazolium salt WST-1 or FACS and conventional RT-PCR or quantitative real-time PCR respectively.

RESULTS: The immortal cells expressed the PSC markers aSMA desmin vimentin GFAP but no epithelial and ductal markers. TGFb1 stimulation resulted in a G1-arrest of the cells as demonstrated by FACS analysis. As shown in WST-1 assays this G1-arrest resulted in a significant decrease of the proliferation of the cells. Furthermore the cells expressed several genes implicated in pancreatic fibrosis and matrix turnover as Collagen type I Fibronectin TGFb1 CTGF MMP-2 and TIMP-1. Apart from MMP-2 all these genes were markedly upregulated by treatment of the cells with TGFb1 findings published for primary activated PSC too.

CONCLUSION: We have immortalized a human pancreatic stellate cell line. The cells retained the phenotypic markers published for native activated pancreatic stellate cells thus these cells

may be useful to analyse the molecular pathomechanisms resulting in the fibrogenesis of the pancreas.

AABO

Oral Presentation

Experimental pancreatitis - Meeting Hall 4 (Room 7)

Monday September 27 2004 11.00-12.30

Abstract: OP-G-33

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EFFECTS OF ANGIOTENSIN II ON RAT PANCREATIC STELLATE CELLS

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INTRODUCTION: Chronic pancreatitis is characterized by the progressive destruction of the exocrine pancreas and its replacement by fibrous tissue. Pancreatic stellate cells (PSCs) were discovered and identified as major source of extracellular matrix protein found in the fibrotic pancreas tissue. The rennin-angiotensin system is frequently activated in patients with chronic disease. Angiotensin II (AT-II) has been suggested to play an important role in pancreatic fibrosis.

AIMS & METHODS: The aim of the present study was to examine the in vivo effect of AT-II on PSCs activation. Rat PSCs were prepared from the pancreas tissues of male Wistar rats as previously described using the Nycodenz solution after perfusion with 0.03% collagenase P. After we incubated PSCs in serum-free medium for 24 hours the medium with or without treatment of AT-II (1 or 10 mmol/L) and AT-II type1 receptor blocker (AT1-RB 0.1 or 1 mmol/L) was changed every day and the cells cultured until day 6. AT-II receptors (AT1-Ra AT1-Rb and AT2-R) transforming growth factor beta (TGF-beta) an important mediator of this matrix expansion and alpha smooth muscle actin (alpha-SMA) immunochemical marker of activation of PSCs was studied by RT-PCR real-time RT-PCR and Western blotting respectively.

RESULTS: AT2-R mRNA of the cells after treatment by AT-II increased. However the mRNA levels of AT1-Ra and AT1-Rb two isoforms of the AT1-R in the rodents did not change. AT-II increased the pancreatic TGF-beta mRNA expression and alpha-SMA protein level and this effect was totally blocked by AT1-RB.

CONCLUSION: We found that AT-II and AT-R interaction played a pivotal role in pancreatic fibrosis development. AT1-RB significantly reduced pancreatic fibrosis through suppressing activated PSCs with concomitant TGF-beta down-regulation. The drug may provide an effective new strategy for antifibrosis therapy.

AABP

Oral Presentation

Experimental pancreatitis - Meeting Hall 4 (Room 7)

Monday September 27 2004 11.00-12.30

Abstract: OP-G-34

0 Citation: Gut 2004; 53 (Suppl VI) A9

SIGNAL TRANSDUCTION OF CERULEIN-INDUCED CYTOKINE EXPRESSION IN PANCREATIC ACINAR CELLS

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INTRODUCTION: The signaling pathways mediating cytokine production in pancreatic acinar cells have not been fully understood. Recent studies indicated that cytokine expression requires activation of NF-{\f1 k}B and AP-1 as well as activation of the MAP kinases. However the precise relationship between transcription factor and MAP kinase remains unclear.

AIMS & METHODS: We examined the requirements of ras MAP kinases NF-{\f1 k}B and AP-1 for cerulein-induced cytokine expresssion in pancreatic acinar AR42J cells. Cerulein was treated to the wild-type cells and the transfected cells with control vector (pcDNA) I{\f1 k}B mutant gene (I{\f1 k}B mt) H-ras mutant gene (Ras N-17) or c-jun dominant negative gene (TAM67). In addition to investigate the role for MAP kinases three subtypes of MAP kinases were measured in the cerulein-treated AR42J cells and we used phamacological inhibitors to attenuate signaling via these kinases.

RESULTS: 1) Cerulein (10-8M) induced production of the inflammatory IL-6 IL-1{\f1 b} and TNF-{\f1 a} mRNA and protein expression in AR42J cell. 2) Inhibition of ras NF-{\f1 k}B and AP-1 using transfected cell with Ras N-17 TAM67 and I{\f1 k}B mutant decrease the cytokine gene expression induced by cerulein (10-8M) as compared to pcDNA cells and the wild-type cells. 3) Cerulein induced NF-{\f1 k}B activation with biphasic kinetics. i.e. NF-{\f1 k}B was strongly activated within 30 min after stimulation and a second phase of NF-{\f1 k}B activation was prominent at 4-6 h. Transfection of Ras N-17 or TAM67 in AR42J cells reduced cerulein-induced NF-{\f1 k}B activation. 4) Cerulein induced the activation of AP-1 within 30 min after stimulation and AP-1 activation was sustained continuously until 6 h. Transfection of Ras N-17 but not I{\f1 k}B mutant reduced cerulein-induced AP-1 activation. 5) Three subtypes of MAP kinases (ERK JNK and p38 MAPK) activities are elevated rapidly by cerulein in AR42J cells 6) Inhibition of MEK activity resulted in a reduction of NF-{\f1 k}B and AP-1 activations and cytokine expressions whereas the inhibition of p38 MAPK did not.

CONCLUSION: Cytokine gene expression by cerulein in AR42J cells is mediated via the activation of the ras MAP kinases NF-{\f1 k}B and AP-1. Ras function as common upstream activators of both NF-{\f1 k}B and AP-1 pathway and AP-1 may be required for activation of NF-{\f1 k}B. AP-1 and/or NF-{\f1 k}B transcription factors are potential downstream mediators of MAP kinases especially ERK in the cerulein-induced cytokine expression in AR42J cell. It is believed that inhibion of signal transduction pathway such as ras MAP kinases NF-{\f1 k}B and AP-1 might alleviated the inflammatory response in pancreatic acinar cells by suppressing cytokine gene expression

AABQ

Oral Presentation

Experimental pancreatitis - Meeting Hall 4 (Room 7)

Monday September 27 2004 11.00-12.30

Abstract: OP-G-35

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MICROARRAY ANALYSIS OF GENE EXPRESSION IN PANCREATIC STELLATE CELLS

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INTRODUCTION: Pancreatic stellate cells (PSC) were defined by an activation process from a quiescent stage to a myofibroblast-like cell type eliciting increased proliferation as well as extracellular matrix synthesis. The molecular mechanisms of this cell transformation are not fully understood. Using the microarray technique we analysed the gene expression profile of PSCs during their activation due to in vitro cultivation.

AIMS & METHODS: PSCs were isolated from the pancreas of Lewis rats using collagenase digestion and density gradient centrifugation. Total RNA of cultivated PSCs was extracted 2 4 7 and 14 days after isolation using the RNeasy Mini Kit (Qiagen). Evaluation of gene expression was carried out by means of the Rat Genome U34 Array (Affymetrix) interrogating 8.850 DNA sequences representing about 7.500 genes. The micro array expression data from MAS 5.0 was analysed with the software system gEn0M using an empirical algorithm for extracting a set of differential expressed genes over time series. Selected genes of interest were subjected to RT-PCR Real Time PCR as well as immunoblotting.

RESULTS: Activated PSCs were defined by high transcript levels of a-smooth muscle actin and of components of the extracellular matrix. While profibrogenic proteins were upregulated during cell activation quiescent PSCs were characterized by high expression levels of immune regulatory mediators. We have focussed on the expression profile and the regulation of the Th2 cytokine IL-10. The PSC transformation process was accompanied by a clear downregulation of IL-10. The transcript levels of IL-10 could be modulated by various cytokines.

CONCLUSION: The results suggest an involvement of pancreatic stellate cells in the regulation of inflammatory processes in the pancreas.

AABR

Oral Presentation

Experimental pancreatitis - Meeting Hall 4 (Room 7)

Monday September 27 2004 11.00-12.30

Abstract: OP-G-36

0 Citation: Gut 2004; 53 (Suppl VI) A9

A C-JUN N-TERMINAL KINASE INHIBITOR SP600125 BLOCKS ACTIVATION OF RAT PANCREATIC STELLATE CELLS

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INTRODUCTION: In response to pancreatic injury and in cell culture pancreatic stellate cells (PSCs) are transformed (\activated\) into highly proliferative myofibroblast-like cells which express alpha-smooth muscle actin and produce extracellular matrix components. Activated PSCs are implicated in the pathogenesis of pancreatic fibrosis and inflammation. The activation of signaling pathways such as p38 mitogen-activated protein kinase (Masamune et al. 2003a) and Rho-Rho kinase (Masamune et al. 2003b) is likely to play a role in PSC activation. However the precise intracellular signaling pathways in PSCs are largely unknown. We here evaluated the effects of SP600125 (anthra [1 9-cd] pyrazole-6 (2H)-one) an inhibitor of c-Jun N-terminal kinase (JNK) on the activation of PSCs.

AIMS & METHODS: PSCs were isolated from rat pancreas tissue and used in their culture-activated myofibroblast-like phenotype unless otherwise stated. Activation of JNK was determined by Western blotting using anti-phosphospecific JNK and c-Jun antibodies. Activation of transcription factors was determined by electrophoretic mobility shift assay. The effects of SP600125 on the key parameters of activation (chemokine production collagen production and proliferation) were examined. The effect of SP600125 on the activation of freshly isolated PSCs in culture was also examined.

RESULTS: Interleukin-1 activated both 46 kDa and 54 kDa JNK whereas platelet-derived growth factor-BB activated only 46 kDa JNK. SP600125 inhibited interleukin-1-induced JNK activity and activator protein-1 activation but did not affect the activation of extracellular-regulated kinase p38 mitogen-activated protein kinase and nuclear factor kB. SP600125 inhibited platelet-derived growth factor-induced proliferation inducible monocyte chemoattractant protein-1 production and serum-induced type I collagen production. Although SP600125 did not inhibit the transformation it attenuated the proliferation of freshly isolated PSCs in culture.

CONCLUSION: Our results suggest a role of JNK in the activation of PSCs and a potential application of JNK inhibitors for the treatment of pancreatic fibrosis and inflammation

Reference: Masamune A et al. (2003a) Inhibition of p38 mitogen-activated protein kinase blocks activation of rat pancreatic stellate cells. J Pharmacol Exp Ther 2003;304:8-14.

Masamune A et al. (2003b) Specific Rho kinase inhibitors block activation of pancreatic stellate cells. Br J Pharmacol 140:1292-1302.

AABS

Oral Presentation

Surgery for benign GI disease - Meeting Hall 5 (Room 8)

Monday September 27 2004 11.00-12.30

Abstract: OP-G-37

0 Citation: Gut 2004; 53 (Suppl VI) A9

ENDOSCOPIC SUTURING FOR TREATMENT OF GERD: A MULTICENTER TRIAL WITH THE BARD ENDOCINCH

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INTRODUCTION: A multicenter prospective study was conducted to assess the safety and efficacy of endoscopic suturing for the treatment of GERD.

AIMS & METHODS: Inclusion criteria were symptomatic GERD (GERD-HRQL>20 without treatment) continuous and effective PPI-therapy for more than 3 months. Exclusion criteria were grade II and more esophagitis hiatal hernia (>2cm) Barrett's achalasia body mass index>40. The following parameters were assessed during the 2 months before procedure: medication use GERD-HRQL score with and without treatment esophageal 24h pHmetry and manometry obtained once PPI were stopped for 10 days gastrointestinal quality of life index. Two sutures (Endocinch BARD) or more were performed on a vertical axis the upper at the level of the Z-line. Re-treatment was permitted after 3 months. The follow-up consisted of questionnaire at 15 days 1 3 6 and 12 months (medication GERD score adverse events) pHmetry manometry and gastroscopy at 3 months gastroscopy at 12 months (mo).

RESULTS: 60 patients (age mean 48y 20 females) were included. A mean of 2.75 sutures per patient was performed. 3 pts had a second procedure. Main adverse event was dysphagia (18%) quickly resolutive. Others were retrosternal pain (7%) and pharyngeal pain (7%). The percentage of patients without PPI was 67% at 3mo 60% at 6m 52% at 12mo. The percentage of patients without or with lower dose of PPI was 74% at 6mo and 64% at 12 mo. The mean GERD-HRQL score was reduced ($p<0.001$). Improvement also was observed in mean GI quality of life index ($p<0.001$). Median esophageal acid exposure improved significantly and 33% of them were

normalized at 3 months. The LOS basal pressure was increased ($p<0.05$). At gastroscopy 49% of initial sutures were still present after 12 mo and 20% of patients did not have anymore.

CONCLUSION: This study demonstrates the safety of this suturing system and its efficacy to reduce symptoms and medication use. However results observed at one year suggests that long term persisting effects are uncertain.

AABT

Oral Presentation

Surgery for benign GI disease - Meeting Hall 5 (Room 8)

Monday September 27 2004 11.00-12.30

Abstract: OP-G-38

0 Citation: Gut 2004; 53 (Suppl VI) A10

ENDOSCOPIC FULL-THICKNESS PLICATION FOR GERD: DURABILITY AT 12 MONTHS

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INTRODUCTION: The Plicator procedure has been designed to inhibit gastroesophageal (GE) reflux by fixating the full-thickness of the cardia wall under direct endoscopic visualization. The resulting serosa-to-serosa tissue union may help to accentuate and restore the valvular mechanism of the GE junction.

AIMS & METHODS: To assess safety efficacy and 12-month durability of endoscopic full-thickness plication in patients with symptomatic GERD. Methods: Patients with chronic heartburn requiring maintenance anti-secretory therapy were recruited. Exclusions were hiatal hernia (>2cm) Grades III and IV esophagitis and Barrett's. The following were assessed at baseline (on and off-meds) and 12 month post-plication: GERD-HRQL GSRS SF-36 questionnaires and medication use. Additionally 24-hr pH-metry and manometry were measured at baseline three-months (pH/manometry) and six-months (pH only) post-plication. All patients received a single full-thickness plication in the gastric cardia 1-2cm below the GE junction.

RESULTS: Sixty-four patients (mean age 46.3 range 23-71) underwent endoscopic full-thickness plication. No re-treatments were performed. One-year post-procedure proton pump inhibitor (PPI) therapy remained completely discontinued in 68% (36/53) of PPI dependent patients and median GERD-HRQL scores (n=57) were improved when compared to baseline off-meds (19.0 vs. 5.0) and on-meds (13.0 vs. 5.0). In 24-hour pH-metry performed at six-months post-procedure (n=46) 80% of patients demonstrated an improvement in distal esophageal acid exposure. Median % time pH < 4 decreased 39% with 30% of patients experiencing a normalization of pH at 6-months. No significant change in esophageal manometry was noted. All

procedure related adverse events occurred acutely including one gastric perforation which was managed conservatively without sequelae. Common adverse events included sore throat (41%) and abdominal pain (20%) resolving spontaneously within several days post-procedure.

CONCLUSION: In this study a single full-thickness plication placed at the GE junction reduced symptoms medication use and esophageal acid exposure associated with GERD. Sustained reduction in PPI use at 1-year follow-up suggests durability of full-thickness tissue apposition.

AABU

Oral Presentation

Surgery for benign GI disease - Meeting Hall 5 (Room 8)

Monday September 27 2004 11.00-12.30

Abstract: OP-G-39

0 Citation: Gut 2004; 53 (Suppl VI) A10

ANTIREFLUX SURGERY FOR NON EROSIVE REFLUX DISEASE: A COMPARATIVE STUDY WITH REFLUX ESOPHAGITIS

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INTRODUCTION: In contrast to erosive reflux disease (ERD) there is a paucity of data concerning results of antireflux surgery (ARS) in non erosive reflux disease (NERD) patients. Furthermore the few studies available focused only on short-term follow-up and essentially in terms of symptom relapse.

AIMS & METHODS: We therefore conducted a retrospective follow-up study to compare the mid-term outcome of patients with and without mucosal breaks at endoscopy before surgery. The assessment was based upon quality of life (QOL) symptomatic relapse and drug intake after surgery. 121 patients (60 without esophagitis and 61 with esophagitis) with symptomatic reflux disease (Symptom Index>50%) were enrolled outside the context of a clinical trial. They were all referred to our laboratory for 24-hour pH monitoring prior to ARS between the 1st January 1995 and 31 December 2002. At the end of follow-up each subject was invited to answer French validated QOL-GERD questionnaire REFLUX-QUAL and a standardized questionnaire for symptoms and therapeutic needs after surgery.

RESULTS: Before surgery ERD and NERD patients did not differ in term of age (47±b113) esophageal acid exposure (10±b15) and symptom index (77±b116 vs} 78±b116). There were more women in the NERD group ($p<0.001$). The symptom pattern was the same in both groups and the indication for surgery was represented by dependence to drug therapy in more than 50% of cases. Laparoscopic surgery and Nissen technique were performed in 89% of patients. After a 36-month median follow-up after surgery NERD patients reported more symptoms than ERD patients (40% {vs} 29% NS). Symptoms were mainly daily (30% {vs} 17% NS). Moreover NERD patients reported significantly more reflux (heartburn and regurgitation) and dyspeptic symptoms (bloating epigastric pain and indigestion). The proportion of patients continuing to take anti-reflux drugs was higher in NERD patients (39% {vs} 25% NS) especially with regard

to PPIs (32% {vs} 10% p<0{.^{0}5). QOL scores tend to be lower in NERD patients (75±b126 {vs} 84±b119 NS) and the difference reached statistical level of significance for \relational life\ dimension (72±b131 {vs} 86±b125 p=0.003). The same results were obtained when analysis was restricted to patients with complete fundoplication (n=108).

CONCLUSION: Although few differences reached the statistical level of significance results of ARS tend to be worse in NERD patients. Our study also confirms that in clinical practice excellent results of ARS are only reported by less than two thirds of patients and that approximatively one third in the NERD group still continue to take anti-reflux medications.

AABV

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A POOR RESPONSE TO PROTON PUMP INHIBITION IS NOT A CONTRA-INDICATION FOR LAPAROSCOPIC ANTI-REFLUX SURGERY FOR GASTRO-OESOPHAGEAL REFLUX DISEASE

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INTRODUCTION: Some centres believe that a poor response to PPIs equates to a poor outcome following Laparoscopic Anti-Reflux Surgery (LARS) and use a response to PPIs as a diagnostic tool for Gastro-Oesophageal Reflux Disease (GORD). We aim to assess what proportion of our surgically treated population with proven reflux disease responded poorly to PPIs and whether a poor response could be used to predict the outcome of LARS.

AIMS & METHODS: Of 390 consecutive patients who underwent LARS between January 1993 and November 2002 324 had complete data and were included in this study. Following standardised assessment patients were asked to record the efficacy of their medical treatment on a visual analogue scale. Pre-operative and post-operative symptom scores were recorded with outcome measured by a modified Visik score. Visik I/II equated to an excellent/good outcome while Visik III/IV equated to a poor/bad outcome.

RESULTS: Median follow-up was 1 year. Patients were separated into 2 groups based on their response to PPIs [Good responders >50% relief (n=233) poor responders <49% relief (n=91)]. Both groups demonstrated a significant fall in symptom scores post-op ($P<0.001$). 218 out of 233 good responders (93.6%) had an excellent or good outcome. The corresponding figures for poor responders were 79 out of 91 (86.8%). There was no significant difference in the proportions of excellent/good to poor/bad outcome in the 2 groups ($P=0.08$ in Chi-square test). 27 patients reported a poor/bad outcome despite a significant fall in post-operative symptom scores ($P<0.001$). The proportion of poor responders did not differ significantly between those with poor/bad outcome (12/27) and those with a excellent/good outcome (79/297) ($P=0.08$ in Chi-square test). Of those with poor/bad outcome 70% (19) underwent post-op pH studies. Of these 7 had positive studies post-op (36.8%) compared to 13/146 with excellent/good outcome (8.2%).

CONCLUSION: Our results do not support the assumption that poor response to PPIs equates to poor outcome after LARS. Patients with poor response to PPIs should not be denied LARS if pH testing is positive.

AABW

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FIVE YEAR'S RESULTS OF A RANDOMIZED CLINICAL TRIAL COMPARING OPEN AND LAPAROSCOPIC NISSEN FUNDOPLICATION

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INTRODUCTION: In 1997 a randomised clinical trial (RCT) was initiated to compare the effectiveness of laparosocpic (LNF) and open conventional Nissen fundoplication (CNF) - the Dutch Antireflux Surgery Study Group. About 200 patients had to be included to answer this question and it was agreed upon to perform an interim analysis after the inclusion of 100 patients with a minimum follow-up of 3 months. The study was prematurely stopped because of an excess of dyspahgia in the laparoscopic group ($p<0.001$). In the discussion to follow the learning curve was an important focus of the crtiticism. At two years the results between the two groups was no longer significant (further treatment included in the analysis!)

AIMS & METHODS: The cohort of 103 patients was followed up and after five years a detailed questionnaire - reflux symptoms general state of health further treatment - was sent to all patients operated to learn about the long-term subjective outcome and about a potential difference between the groups.

RESULTS: 84% of the questionnaires were returned (no response because of: bad result 2; fully asymptomatic 1 address unknown 7 died 1 unknown 9). As for reflux symptoms: LNF: 50% asymptomatic 48% sign. improved; CNF: 53% 35% resp. (n.s.); general state of health: LNF: 70% improved 20% simliar 10% deteriorated for CNF 88% 5% 7% resp. (n.s.) As for medication LNF: 11% PPI 2% H2RA 2% prokinetics for CNF 5% 3% 1% resp. (n.s.) Successful outcome (=no further treatment needed) for LNF: 93% redo surgery included 76% redo excluded for CNF: 91% 74% resp. Overall success of surgical treatment for both groups if based on reflux symptoms: 87% based on general state of health: 75% free from medication: 71% free from reintervention: 75%. At five years there were no differences between both groups in terms of symptomatic outcome genertal state of health need for medical treatment or reintervention.

CONCLUSION: Considering that the majority had \refractory GERD as the indication for surgery the over-all outcome is satisfactory. \Unwillingness to take life-long medication\ is still a

controversial indication for surgery. The relatively high need for further treatment should be part of the prfteoperative information. The inital suggestion of the dominant role of the learniong curve probasbly not completed by the authors is masked by further long-term evaluation

AABX

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LAPAROSCOPIC HELLER-DOR OPERATION REMAINS AN EFFECTIVE TREATMENT FOR ESOPHAGEAL ACHALASIA AT A MINIMUM 6-YEAR FOLLOW-UP

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INTRODUCTION: Short to mid-term satisfactory results after laparoscopic myotomy for achalasia are reported in about 90% of treated patients. However long-term studies are lacking and a far less favourable outcome has been reported at a minimum 4-year follow-up after both traditional thoracotomic myotomy and pneumatic dilation[1].

AIMS & METHODS: In this study we reviewed the long-term symptomatic results of Heller-Dor laparoscopic operation in patients operated in our institution between 1992 and 1998.

RESULTS: Our study population consists in 63 patients with a minimum 6-year follow up (median 94 months range 72-131). There were 31 males and 32 females with a median age of 39 years (range 15-73). As part of the regular follow-up these patients have been seen 1 and 6 months after the operation (when barium swallow endoscopy manometry and pH-monitoring were performed) and then every year. Patients who failed to show-up at the clinic were contacted on the phone. A dedicated symptom-score based on severity and frequency of symptoms (dysphagia regurgitation pain and heartburn) was used. Moreover the Eckardt score was calculated. GERD symptoms and the presence of esophagitis were also investigated and recorded. In these patients the median symptom score decreased from 16 (range 7-22) preoperatively to 4 (range 0-18) at the last follow-up $p<0.01$. Similarly the Eckardt score decreased from 7 (range 3-11) to 1 (range 0-6) $p<0.01$. Twelve patients referred a symptom score higher than the 10th percentile of the preoperative symptom score (i.e.: 8) and/or a post-operative Eckardt score of more than 3 and therefore were considered as failures: 9 of them were already diagnosed at a very early follow-up (less than one year after surgery) and had received pneumatic dilations. Six patients reported mild GERD symptoms well controlled by PPIs therapy. In overall after a minimum 6-year time interval from the operation 81% of the patients were still satisfied with the treatment and had a normal eating capability.

CONCLUSION: This study demonstrated that the long-term outcome of laparoscopic surgical treatment of esophageal achalasia is only marginally affected by the length of the follow-up and it is much better than what has been reported both for traditional surgery (33%) or dilations (26%). Most of the symptomatic failures do occur early and only a minority of patients actually worsen with the passing of the time.

Reference: Torbey CF et al. J Clin Gastroenterol 1999;28:125

AABY

Oral Presentation

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RANDOMIZED CLINICAL TRIAL OF ITOPRIDE FOR THE TREATMENT OF POSTOPERATIVE ILEUS AFTER LAPAROSCOPIC CHOLECYSTECTOMY

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INTRODUCTION: Postoperative ileus is a distressing and frequent adverse effect after laparoscopic cholecystectomy (LCE). The goal of this prospective study was to evaluate if the new prokinetic drug itopride hydrochloride (Ganaton±ae Abbott GmbH Co. KG Wiesbaden SRN) may ameliorate the gastric motility in the early post-operative period after LCE.

AIMS & METHODS: 50 patients undergoing LCE were observed. The patients were perorally treated with itopride hydrochloride (50 mg per day) or placebo (sacharose) in a randomized double-blind mannever. EGG records were done 6 24 and 48 h after surgery. EGG was performed in a fasting state and after stimulation with a liquid bolus. The EGG data were recorded by a Microdigitrapper device and analyzed using spectral analysis and Fourier transformation.

RESULTS: When comparing both groups (itopride and placebo) nausea was found significantly more frequently in the placebo group at the day of surgery as well as on postoperative days 1 and 2. The incidence of vomiting did not differ between both groups. Moreover there are earlier return of physiologic EGG curve in itopride group.

CONCLUSION: The perioperative use of itopride accelerates the normalization of the EGG curve after LCE. Itopride was well tolerated and we did not observe serious adverse effects during therapy. Our data suggests that itopride can be a useful accelerator of postoperative ileus restoration after LCE.

Part of study supported by grant of IGA Nr 8152-3

Reference: G±fcrlich R. Frasko R. Maruna P. Chachkhiani I.: Randomized clinical trial of itopride for the treatment of postoperative ileus after laparoscopic cholecystectomy. Chir Gastroenterol. 2004 ro±e8. 20 s. 61-65.

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