The Effect of Genetic Polymorphisms of Cyclooxygenase 2 on Acute Pancreatitis in Turkey.

Ozhan G, Yanar TH, Ertekin C, Alpertunga B.

Department of Pharmaceutical Toxicology, Faculty of Pharmacy, Istanbul University, Istanbul, Turkey.

The aims of this study was to determine if polymorphisms in the cyclooxygenase 2 (COX-2) gene is associated with acute pancreatitis (AP) and to evaluate if inflammation risk is associated with specific COX-2 gene haplotypes containing these polymorphisms. The COX-2 genotypes for 7 polymorphisms (rs5275, rs2206593, rs4648262, rs4648261, rs2066826, rs5277, rs2745557) were determined using polymerase chain reaction-restriction fragment length polymorphism analysis in 103 patients with AP and 92 healthy controls. Except for rs5275, the frequencies of COX-2 polymorphisms were both similar in patients with mild or severe pancreatitis, so were in pancreatitis patients and in controls. Only rs5275 was statistically significantly associated with AP risk. The association was seen with rs5275 (P=0.03); specifically, patients carrying the TT genotype in comparison with patients carrying the CC genotype had a significantly lower risk of disease (odds ratio, 1.88; 95% confidence interval, 1.06-3.34). Haplotypes with nucleotide T at the -18491961 position (rs5275) and A at the 184915627 position (rs4648261) of COX-2 promoter seem to increase susceptibility (odds ratio, 2.46; 95% confidence interval, 1.15-5.29; P=0.02). These findings suggest that the rs5275 polymorphism in the 3'-untranslated region of the COX-2 gene may be used as marker for defining the risk of AP.

Binge Drinking Aggravates the Outcomes of First-Attack Severe Acute Pancreatitis.

Deng L, Xue P, Huang L, Yang X, Wan M, Xia Q.

Department of Integrated Traditional Chinese and Western Medicine, West China Hospital, Sichuan University. Chengdu, People's Republic of China.

The authors studied the association of binge drinking and the outcomes of severe acute pancreatitis (SAP). This retrospective study included 347 patients with first-attack SAP from January 2001 to February 2004. On the basis of the history of binge drinking or not, the patients were divided into the alcohol (n=77) and the control groups (n=270). Clinical data of the two groups were compared. Patient age and comorbidity were similar between the two groups. There were more men (64, 83.1%) than women (13, 16.9%; P<0.05) in the alcohol and the control groups (111, 41.1%; P<0.05). The two groups had significant differences in admission serum triglyceride levels (5.0±5.0 vs. 3.0±3.5, P<0.05), Balthazar computed tomographic score (6.3±5.4 vs. 4.2±4.5, P<0.05), and Acute Physiology and Chronic Heath Evaluation II score (19.1±5.1 vs. 16.2±6.0, P<0.05). Total mortality and the incidences of complications were higher in the alcohol group than in the control group (P<0.05). In conclusion, binge drinking might be a contributor to the aggravation of first-attack SAP.
Intestinal Barrier Dysfunction in a Randomized Trial of a Specific Probiotic Composition in Acute Pancreatitis.


Department of Surgery, University Medical Center Utrecht, Utrecht, The Netherlands.

The authors aimed to determine the relation between intestinal barrier dysfunction, bacterial translocation, and clinical outcome in patients with predicted severe acute pancreatitis and the influence of probiotics on these processes. The authors carried out a randomized, placebo-controlled, multicenter trial on probiotic prophylaxis (Ecologic 641) in patients with predicted severe acute pancreatitis (PROPATRIA). Excretion of intestinal fatty acid binding protein (IFABP), a parameter for enterocyte damage, recovery of polyethylene glycols (PEGs, a parameter for intestinal permeability), and excretion of nitric oxide (NOx, a parameter for bacterial translocation) were assessed in urine of 141 patients collected 24 to 48 h after start of probiotic or placebo treatment and 7 days thereafter. IFABP concentrations in the first 72 h were higher in patients who developed bacteremia (P=0.03), infected necrosis (P=0.01), and organ failure (P=0.008). PEG recovery was higher in patients who developed bacteremia (PEG 4000, P=0.001), organ failure (PEG 4000, P<0.0001), or died (PEG 4000, P=0.009). Probiotic prophylaxis was associated with an increase in IFABP (median 362 vs. 199 pg/mL; P=0.02), most evidently in patients with organ failure (P=0.001), and did not influence intestinal permeability. Overall, probiotics decreased NOx (P=0.05) but, in patients with organ failure, increased NOx (P=0.001). In conclusion, bacteremia, infected necrosis, organ failure, and mortality were all associated with intestinal barrier dysfunction early in the course of acute pancreatitis. Overall, prophylaxis with this specific combination of probiotic strains reduced bacterial translocation, but was associated with increased bacterial translocation and enterocyte damage in patients with organ failure.

Endoscopic Treatment for Chronic Pancreatitis: Indications, Technique, Results.

Hirot a M, Asakura T, Kanno A, Shimosegawa T.

Division of Gastroenterology, Tohoku University Graduate School of Medicine. Sendai, Japan.

Endoscopic treatment associated with or without extracorporeal shock wave lithotripsy (ESWL) for chronic pancreatitis has been employed for about 20 years. Although two randomized control trials have revealed the greater effectiveness of surgery as compared to endoscopic treatment for chronic pancreatitis, a considerable number of patients have successfully obtained complete and long-term relief from pain by the less invasive endoscopic treatment. In this review, the authors discuss the indications, techniques and results of endoscopic treatment and ESWL for painful chronic pancreatitis. The authors also discuss the characteristic clinical features that are predictive of a good response to endoscopic treatment and ESWL.

Efficacy of Endoscopic Ultrasound-Guided Celiac Plexus Block and Celiac Plexus Neurolysis for Managing Abdominal Pain Associated With Chronic Pancreatitis and Pancreatic Cancer.


Division of Gastroenterology and Hepatology, SUNY Downstate Medical Center Maimonides Medical Center. Brooklyn, NY, USA.

Endoscopic ultrasound (EUS)-guided celiac plexus block (CPB) and celiac plexus neurolysis (CPN) have become important interventions in the management of pain due to chronic pancreatitis and pancreatic cancer. However, only a few well-structured studies have been performed to evaluate their efficacy. Given limited data, their use remains controversial. Herein, the authors evaluate the efficacy of EUS-guided CPB and CPN in alleviating chronic abdominal pain due to chronic pancreatitis and pancreatic cancer respectively. Using MEDLINE, PubMed, and EMBASE databases from January 1966 through December 2007, a thorough search of the English literature for studies evaluating the efficacy of EUS-guided CPB and CPN for the management of chronic abdominal pain due to chronic pancreatitis and pancreatic cancer was conducted, along with a hand search of reference lists. Studies that involved less than 10 patients were excluded. Data on pain relief was extracted, pooled, and analyzed. A total of 9 studies were included in the final analysis. For chronic pancreatitis, 6 relevant studies were identified, comprising a total of 221 patients. EUS-guided CPB was effective in alleviating abdominal pain in 51.46% of patients. For pancreatic cancer, 5 relevant studies were identified with a total of 119 patients. EUS-guided CPN was effective in alleviating abdominal pain in 72.54% of patients. EUS-guided CPB was 51.46% effective in managing chronic abdominal pain in patients with chronic pancreatitis,
but warrants improvement in patient selection and refinement of technique, whereas EUS-guided CPN was 72.54% effective in managing pain due to pancreatic cancer and is a reasonable option for patients with tolerance to narcotic analgesics.

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High-Dose Naproxen Aggravates Pancreatic Fibrosis in a Rat Model of Chronic Pancreatitis.


Division of Field Medicine, Department of Internal Medicine, Shanghai Hospital, Second Military Medical University, Shanghai, People's Republic of China.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely prescribed for the treatment of pain in chronic pancreatitis (CP). This study aimed to investigate the effect of NSAIDs on the inflammation and fibrosis progression in trinitrobenzene sulfonic acid-induced CP rats. Chronic pancreatitis was induced by trinitrobenzene sulfonic acid infusion into rat pancreatic ducts. Naproxen treatment (20 and 40 mg/kg per os and intraperitoneally) started 2 weeks after the induction of CP for 3 weeks. Histological analysis of the pancreas, Van Gieson staining, and contents of hydroxyproline were used to evaluate pancreatic damage and fibrosis. Furthermore, the effect of naproxen on nociceptive reflexive behaviors and serum tumor necrosis factor alpha concentration were studied, and immuno-histochemical analysis of alpha-smooth muscle actin in the pancreas was performed. Pancreatic collagen content and alpha-smooth muscle actin expression were higher in the CP group treated with high-dose (40 mg/kg per os) naproxen (P<0.05). High-dose naproxen administered orally aggravated pancreatic fibrosis and inflammation (P<0.05). Instead of playing an analgesic role, high-dose naproxen decreased the thermal withdrawal latencies in CP rats (P<0.05). In conclusion, high-dose naproxen treatment (40 mg/kg per os) aggravated pancreatic fibrosis in CP rats and played an algogenic role that suggests the potential risk of long-term use of NSAIDs as analgesic in clinical practice with CP.

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Overexpression of Smad6 Exacerbates Pancreatic Fibrosis in Murine Caerulein-Induced Chronic Pancreatic Injuries.

Miyamoto T, Nakamura H, Nagashio Y, Asaumi H, Harada M, Otsuki M.

Third Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan.

The authors examined the effect of the overexpression of Smad6 on pancreatic fibrosis after chronic pancreatic injury. Chronic pancreatic injury was induced in transgenic mice overexpressing Smad6 (Tg mice) in acini and wild-type (Wt) mice by 3 episodes of acute pancreatitis per week for 1 to 4 consecutive weeks. Acute pancreatitis was elicited by 6 intraperitoneal injections of caerulein (Cn) at 50 mg/kg of body weight at hourly intervals. Pancreatic fibrosis was evaluated by histological examination and hydroxyproline content before and 1, 2, 3, and 4 weeks of repetitive episodes of Cn-induced acute pancreatitis. The authors further determined transforming growth factor beta1 (TGF-beta1) messenger RNA expression and trypsin activity in the pancreas. After repetitive episodes of acute pancreatitis, pancreatic fibrosis in Tg mice was significantly severer than that in Wt mice at all time points (weeks 1-4). The expression of TGF-beta1 messenger RNA and the activity of trypsin in the pancreas in the Tg mice were significantly high compared with those in the Wt mice at all corresponding time points after repetitive episodes of acute pancreatitis. These results demonstrated that overexpression of Smad6 in acini enhanced the development of pancreatic fibrosis after chronic pancreatic injury.


Frequency of Extrapancreatic Neoplasms in Intraductal Papillary Mucinous Neoplasm of the Pancreas: Implications for Management.

Reid-Lombardo KM, Mathis KL, Wood CM, Harmsen WS, Sarr MG.

Departments of Surgery and Health Sciences Research, Mayo Clinic, Rochester, MN, USA.

The authors aimed to estimate the frequency of extrapancreatic neoplasms in patients with IPMN compared with those with ductal pancreatic cancer and a general referral population. Several studies have reported an increased risk of extrapancreatic neoplasms in patients with IPMN, but these studies focused only on those patients who underwent resection and excluded those patients treated nonoperatively. All patients diagnosed with IPMN at Mayo Clinic from 1994 to 2006 were identified. Two control groups consisting of Group 1 (patients with a diagnosis of ductal pancreatic adenocarcinoma, 1:1) and Group 2 (a general referral population, 3:1) were matched for gender and age at diagnosis, year of registration, and residence. Logistic regression was used to assess the risk of a diagnosis of extrapancreatic neoplasms among cases versus controls. There were 471 cases, 471 patients in Group 1, and 1,413 patients in Group 2. The proportion of IPMN patients having any extrapancreatic neoplasm diagnosed before or coincident to the index date was 52% (95% CI, 47-56%), compared
with 36% (95% CI, 32-41%) in Group 1 (P<0.001), and 43% (95% CI, 41-46%) in Group 2 (P=0.002). Benign neoplasms most frequent in the IPMN group were colonic polyps (n=114) and Barrett's neoplasia (n=18). The most common malignant neoplasms were nonmelanoma skin (n=35), breast (n=24), prostate (n=24), colorectal cancers (n=19), and carcinoid neoplasms (n=6). In conclusion, patients with IPMN have increased risk of harboring extrapancreatic neoplasms. Based on the frequency of colonic polyps, screening colonoscopy should be considered in all patients with IPMN.


Consensus Report of the National Cancer Institute Clinical Trials Planning Meeting on Pancreas Cancer Treatment.

Karmanos Cancer Institute, Wayne State University. Detroit, MI, USA.

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer mortality, despite significant improvements in diagnostic imaging and operative mortality rates. The 5-year survival rate remains less than 5% because of microscopic or gross metastatic disease at time of diagnosis. The Clinical Trials Planning Meeting in pancreatic cancer was convened by the National Cancer Institute's Gastrointestinal Cancer Steering Committee to discuss the integration of basic and clinical knowledge in the design of clinical trials in PDAC. Major emphasis was placed on the enhancement of research to identify and validate the relevant targets and molecular pathways in PDAC, cancer stem cells, and the microenvironment. Emphasis was also placed on developing rational combinations of targeted agents and the development of predictive biomarkers to assist selection of patient subsets. The development of preclinical tumor models that are better predictive of human PDAC must be supported with wider availability to the research community. Phase III clinical trials should be implemented only if there is a meaningful clinical signal of efficacy and safety in the phase II setting. The emphasis must therefore be on performing well-designed phase II studies with uniform sets of basic entry and evaluation criteria with survival as a primary endpoint. Patients with either metastatic or locally advanced PDAC must be studied separately.


Randomized Phase II Study of Gemcitabine Administered at a Fixed Dose Rate or in Combination with Cisplatin, Docetaxel, or Irinotecan in Patients with Metastatic Pancreatic Cancer: CALGB 89904.

Dana-Farber Cancer Institute. Boston, MA, USA.

The relative value of gemcitabine-based combination chemotherapy therapy and prolonged infusions of gemcitabine in patients with advanced pancreatic cancer remains controversial. The authors explored the efficacy and toxicity of gemcitabine administered at a fixed dose rate or in combination with cisplatin, docetaxel, or irinotecan in a multi-institutional, randomized, phase II study. Patients with metastatic pancreatic cancer were randomly assigned to one of the following four regimens: gemcitabine 1,000 mg/m² on days 1, 8, and 15 with cisplatin 50 mg/m² on days 1 and 15 (arm A); gemcitabine 1,500 mg/m² at a rate of 10 mg/m²/min on days 1, 8, and 15 (arm B); gemcitabine 1,000 mg/m² with docetaxel 40 mg/m² on days 1 and 8 (arm C); or gemcitabine 1,000 mg/m² with irinotecan 100 mg/m² on days 1 and 8 (arm D).

Patients were observed for response, toxicity, and survival. Two hundred fifty-nine patients were enrolled onto the study, of whom 245 were eligible and received treatment. Anticipated rates of myelosuppression, fatigue, and expected regimen-specific toxicities were observed. The overall tumor response rates were 12% to 14%, and the median overall survival times were 6.4 to 7.1 months among the four regimens. Gemcitabine/cisplatin, fixed dose rate gemcitabine, gemcitabine/docetaxel, and gemcitabine/irinotecan have similar antitumor activity in metastatic pancreatic cancer. In light of recent negative randomized studies directly comparing several of these regimens with standard gemcitabine, none of these approaches can be recommended for routine use in patients with this disease.