Biliary tract

PROBABILITY OF DEVELOPING GALLSTONES AND RELATED RISK FACTORS IN 400 CIRRHOTICS.


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Background: Several studies have described an increased prevalence of gallstones (GS) in cirrhosis; furthermore, an annual incidence of 2.0% (1) and a global cumulative incidence of 7.3-10.0% in 100 patients have been recently (2) been reported.

Aim: To estimate the probability of GS development and related risk factors in 400 patients with different etiologies, GS free at enrollment.

Patients: 400 patients (257 men and 143 women; mean age 58 ± 6 SD 10 yr. and 51 ± 10 yr., respectively) with cirrhosis related to alcohol abuse (n=169), HBV or HCV chronic infection (n=138), HBV or HCV chronic infection (n=196) and alcohol abuse (n=50) and miscellaneous (n=43). At enrollment 241 patients were in Child's A class, 130 in B and 39 in C. Follow up consisted of clinical examination, ultrasonography and ultrasound liver scan (US) every 6 months. Diagnosis of GS was based on consistent US findings or emergency cholecystectomy for GS.

Methods: The cumulative probability of developing GS was estimated by the Kaplan-Meier method. Possible risk factors for GS were studied by logistic regression analysis which included the following variables: sex, age, body mass index (BMI), alcohol intake, Child's class, etiology of cirrhosis, HBAg, albumin, bilirubin, ALT, AST, yGT, alkaline phosphatase, cholesterol, triglycerides.

Results: The median duration of follow up was 48 mo. (range 6-32). 94 patients (23.5%) developed GS. The cumulative probability of developing GS according to years of follow up is given in the table.

Follow up (yr) 0 2 4 6 8
Probability (%) 55 22 15 12 8

The risk of developing GS increased significantly with BMI (p<0.001, odds ratio 2.16) and was significantly higher in women than in men (p<0.001, odds ratio 2.16) and in Child's class B/C than A (p<0.001 in both cases with odds ratio of 2.84 and 5.55 respectively).

Conclusions: In terms of both prevalence (3) and incidence, cholestolithiasis represents a major problem in cirrhosis and an accurate follow up of cirrhotic patients, GS free at enrollment, is mandatory.


INTRACELLULAR SECOND MESSENegORS RESTORE THE IMPAIRED CONTRACTILITY OF HUMAN GALLBLADDER WITH CHOLESTEROL STONES. P.R. Yu, P. Biancani AND J.Behar. Department of Medicine, Rhode Island Hospital, Brown University Medical School, Providence, R.I. U.S.A.

Previous studies have shown that human gallbladders with cholesterol stones (CS) have a weak contraction in response to the octapeptide of cholecystokinin (CCK-8). In contrast, gallbladders with pigment stones (PS) appear to have a normal or increased CCK response. The mechanisms of gallbladder muscle contraction is mediated by two pathways: (1) the action of low concentrations of CCK (10-13 M) is mediated by intracellular calcium (IP-3), which releases calcium from the diacylglycerol (DAG)-protein kinase C (PKC) pathway; (2) high concentrations of CCK (10-5 M) also act through IP-3 and intracellular calcium which then activates the calmodulin (CaM) and light myosin chain kinase pathway. The aim of these studies was to examine the functional integrity of the intracellular pathways that mediate CCK induced contraction in muscle cells from specimens with CS. Sixteen gallbladders with cholesterol and fourteen with pigment stones were included in these studies. All patients had the gallbladders removed electively and none had a history of acute cholelithiasis. Studies were performed in experimentally digested intact or permeabilized smooth muscle cells. Muscle cells were permeabilized by exposure to saponin (75 mg/kg for 4 minutes). Dose-response studies with CCK-8 (10-10-10-8 M) showed that the contraction of muscle cells from gallbladders with PS was greater than that of muscle cells from specimens with CS (p<0.05). Dose-response studies with IP-3 (10-10-10-5 M), DAG (10-13-10-7 M) and CM (10-13-10-5) all increased the contractility of muscle stones from cholesterol stones compared to the contraction induced by CCK (p<0.05). In contrast, there was no difference between the contraction induced by the second messenger and by CCK in muscle cells from gallbladders with PS. There was also no difference between the contraction of muscle cells from specimens with CS and from specimens with PS in response to IP-3, DAG and CM. The CCK induced contraction appears to be mediated by G protein since it was almost completely blocked by a specific antibody against the a3 subunit. GPS (10-5-10-4 M), the non-selective GTP, also increased the contractility of muscle cells from gallbladders with CS to levels similar to those from specimens with PS. It is concluded that the contractility of muscle cells from specimens with CS is restored by activating the postmembrane contractile pathways and the muscle defect may be due to abnormal receptor function and/or abnormal interaction between receptors and G proteins.

CLOSING AND FUNCTIONAL EXPRESSION OF A CCK-B RECEPTOR FROM GUINEA PIG GALLBLADDER. A. de Marchi, JR Pinho, SA Runk, Digestive Diseases Branch, HMDI, National Institutes of Health, Bethesda, MD 20892

The contractile response to cholecystokinin (CCK) on isolated smooth muscle cells may be mediated by two distinct CCK receptor subtypes, one CCK preferring and the other gastrin preferring. We have recently isolated a CDNA from guinea pig gallbladder with sequence homology to the rat CCK receptor subtype. Its receptor expression pharmacology is consistent with the physiological data for a CCK preferring receptor. We screened a guinea pig gallbladder cDNA library with a 32p labelled, rat CCK receptor CDNA coding sequence probe in order to identify a second CCK receptor subtype with gastrin preferring pharmacology. The two longest CDNA clones identified (2.9 kb insert) contained a single long reading frame encoding a 1.1 kb protein with 30% homology with the rat CCK receptor and a calculated molecular weight of 48,2 KDa. Hydropathy analysis indicates seven regions of hydrophobic residues corresponding to putative transmembrane domains expected for members of the G-protein-coupled superfamiy of receptors. The sequence allows for three potential N-linked glycosylation sites in the extracellular amino terminus. Expression analysis of the receptor CDNA subcloned into the mammalian expression vector pCDL-SR-Alpha and transiently expressed in COS-7 cells showed specific and saturable binding of 125I-Bolton-Hunter labelled CCK-B (125I-BH-CCK). CCK-B and gastrin 17-inhibited binding with nearly equal potency (IC50 = 1 nM) and was nearly linearly increased with increasing concentrations of CCK-B receptor antagonist L 364,718. These results are similar to results seen for native CCK-B receptor in brain and gastric glands and is consistent with CCK receptor subtype. Conclusion: These studies demonstrate that in addition to a CCK-B receptor subtype, a second CCK receptor expressing a second CCK receptor with a typical CCK receptor subtype pharmacology.
OXIII/693

PROMOTION OF GALLBLADDER EMPTYING AND CHOLECYSTOKININ RELEASE BY RAPID INTRAVENOUS ADMINISTRATION OF AMINO ACIDS. G Zoli, A Ballinger, J Healy, LJD O'Donnell, ML Clark, MJG Farthing. Deps. Gastroenterology & Radiology, St Bartholomew's Hospital, London, UK & I Medical Pathology, University of Bologna, Italy.

Patients receiving total intravenous nutrition have iner gallbladders and as a consequence develop gallbladder sludge and gallstones; these can be prevented by enhancing gallbladder emptying. We have explored the efficacy of rapid infusions of intravenous amino acids (IVAAs) in enhancing cholecystokinin (CCK) release and gallbladder contraction, and determined the minimum infusion regimen capable of producing gallbladder emptying.

Eight healthy fasted subjects on four mornings received in random order four different infusion regimens of IVAA mixture (Synthamin 14, RSI amino acids). Gallbladder volumes were determined by ultrasonography before and at 5 min intervals for 60 min after commencing the infusion. Blood was obtained by an indwelling i.v. cannula before and at 10, 20, 30, 45 and 60 min after the start of the infusion. Plasma CCK was measured by radioimmunoassay after separation of the various IVAA regimens were 61.0±12.5% with 250ml in 30 min, 76.8±8.5 with 250ml in 10 min, 63.6±8.4 with 125ml in 5 min, and 24.4±8.0 with 50ml in 5 min. The latter regimen produced significantly less emptying than the other two regimens (p<0.05). Plasma CCK concentrations were not significantly different with infusions of 250ml in 30 min (mean 5.9±1.1 pmol/ml, 211.3±32 pmol/ml (60 min, respectively) 250ml in 10 min (8.2±0.5, 235.6±6.13), 125ml in 5 min (7.0±0.7, 192.9±2.0), but were significantly lower with the infusion of 50ml in 5 min (2.1±0.2, 82.4±6.3; p<0.001).

Intermittent rapid infusion of IVAAs in a load as low as 125ml in 5 min promotes CCK release and gallbladder emptying and should prove useful therapeutically, not only during intravenous nutrition, but also in other situations involving gallbladder inertia, such as critically ill patients in intensive care units and during the post-operative.