E-mail Correspondence with the Food and Drug Administration (FDA) regarding an exemption for an Investigational New Drug (IND) Application

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From: xxx

Sent: Friday, April 05, 2013 8:23 AM

To: xxx

Cc:

Subject: FW: Rectal Indomethacin for Patients Undergoing ERCP

Dear xxx:

We have received, on March 19, 2013, your e-mail dated March 19, 2013, for Indocin Suppositories. This submission contains a protocol titled, "Rectal Indomethacin in the Prevention of Post-ERCP Pancreatitis in High Risk Patients: Searching for the Optimal Dose. A Prospective, Randomized Trial" and a request for exemption from the requirement to conduct the study under an Investigational New Drug Application.

After reviewing the information contained in your submission, we have concluded that your study meets all of the requirements for exemption from the IND regulations and, therefore, an IND is not required to conduct your investigation.

Rectal Indomethacin in the Prevention of Post- ERCP Pancreatitis in High Risk Patients: Searching for the Optimal Dose. A Prospective, Randomized Trial

Protocol Version 8.0

Evan L. Fogel, MD
Professor of Medicine
Indiana University

Richard S. Kwon, MD
Assistant Professor of Medicine
University of Michigan

James Scheiman, MD
Professor of Medicine
University of Michigan

Grace Elta, MD
Professor of Medicine
University of Michigan

Nalini Guda, MD
Clinical Associate Professor of Medicine
University of Wisconsin

Glen Lehman, MD
Professor of Medicine
Indiana University

Stuart Sherman, MD
Professor of Medicine
Indiana University

Paul Tarnasky, MD
Clinical Associate Professor of Medicine
University of Texas Southwestern

B. Joseph Elmunzer, MD
Associate Professor of Internal Medicine
Medical University of South Carolina

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A. Objective: To compare the efficacy of two different dose regimens of prophylactic rectally-administered indomethacin on the incidence on post-endoscopic retrograde pancreatography (ERCP) pancreatitis (PEP) in high-risk patients.

B. Hypotheses and Specific Aims

H1 (primary): A higher peri-procedure dose of rectal indomethacin at ERCP will reduce the incidence of PEP in high risk patients, compared with standard dosing.

H2 (secondary): A higher peri-procedure dose of rectal indomethacin at ERCP will reduce the incidence of moderate to severe PEP in high risk patients, compared with standard dosing.

SA1 (primary): To perform a prospective, randomized, double-blind clinical trial comparing a higher dose indomethacin regimen to standard dosing in preventing PEP in high-risk patients.

SA2 (secondary): In the same format as SA1, to compare a higher dose indomethacin regimen to standard dosing in preventing moderate to severe PEP in high-risk patients.

C. Background, preliminary data, and significance

Pancreatitis is the most frequent complication of endoscopic retrograde cholangiopancreatography (ERCP), accounting for substantial morbidity, occasional mortality, and increased health care expenditures (1-3). Multiple pharmacologic agents have been evaluated in the prevention of post-ERCP pancreatitis (PEP) (4). Recently, interest has developed in the study of non-steroidal anti-inflammatory drugs (NSAIDs) for the prevention of PEP. Mechanistically, NSAIDs are potent inhibitors of phospholipase A2, prostaglandins, and neutrophil/endothelial interaction, all believed to play an important role in the pathogenesis of acute pancreatitis (5-7). Animal models have demonstrated that NSAIDs can reduce mortality associated with pancreatitis (8-10) and a small human trial of indomethacin in non-ERCP acute pancreatitis showed improvement in clinical outcomes (11).

NSAIDs are attractive in the pharmacologic prevention of PEP because they are widely available, inexpensive, and easily administered. In addition, they appear to have a favorable risk profile when given as a one-time dose to appropriately selected patients. Prospective clinical trials evaluating the use of NSAIDS in ERCP have shown that the incidence of adverse events attributable to NSAIDs, including post-procedure hemorrhage, is equivalent in the NSAIDs and placebo groups (12-17). This observation is congruent with previously published data suggesting that NSAIDs in standard doses do not increase the risk of significant bleeding after biliary sphincterotomy (3,18).

Several prospective clinical trials have evaluated rectal NSAIDs in the prevention of PEP (12-15,17). Murray et al. (12) demonstrated a statistically significant benefit of rectal diclofenac in 220 patients who either underwent pancreatography or had manometrically documented sphincter of Oddi dysfunction (SOD). Conversely, Sotoudehmanesh et al. (13) failed to show prophylactic benefit of rectal indomethacin in 442 mostly low-risk patients. A *post hoc* subgroup analysis of this study, however, did reveal a protective effect in patients undergoing pancreatic duct injection, although the power of this subgroup was insufficient to draw concrete clinical conclusions. Khoshbaten et al. (14) showed a statistically significant benefit of rectal diclofenac in 100 patients undergoing pancreatography and Montano Loza et al. (15) also demonstrated a benefit in 150 patients at low-risk for PEP receiving rectal indomethacin or placebo. A meta-analysis of these four studies evaluating rectal NSAIDs in preventing post-ERCP pancreatitis revealed a statistically significant 64% reduction in PEP, with a number needed to treat to prevent one episode of pancreatitis of 15 patients (19). Although the results of this meta-analysis were encouraging, several limitations were noted. First, the component studies enrolled patients at variable risk for PEP. As such, it remained unclear from these data whether rectal NSAIDs were effective in both high and low risk patients, and if so, which group derived the most favorable risk & cost-benefit ratios. Second, the meta-analysis included outcomes from studies evaluating either diclofenac or indomethacin. While these drugs demonstrate similar

phospholipase A2 inhibition in vivo, it remains unclear if both drugs are independently clinically effective (20,21). Moreover, prior positive meta-analyses of prophylactic agents in preventing PEP have subsequently been disproved by additional rigorous clinical investigation (22,23). Therefore, a definitive clinical trial evaluating rectal indomethacin in the prevention of PEP was needed to confirm the results of the meta-analysis (19) and establish a concrete role for prophylactic rectal NSAIDs in clinical practice.

In order to specifically address this issue, Elmunzer and colleagues recently evaluated the role of rectal indomethacin in the prevention of PEP in high-risk patients (17). This multicenter, randomized, placebo-controlled, double-blind clinical trial assigned high-risk patients (82% had suspected or confirmed SOD) to receive a single dose (100mg) of rectal indomethacin or placebo (a glycerin suppository) immediately after ERCP. Post-ERCP pancreatitis developed in 27/295 patients (9.2%) in the indomethacin group compared with 52/307 (16.9%) in the placebo group (p=0.005). This beneficial effect of indomethacin was seen across all subgroups analyzed. Furthermore, moderate-to-severe pancreatitis rates were significantly lower in the indomethacin group (4.4% vs 8.8%, p=0.03). Adverse events were uncommon, as clinically significant bleeding occurred in 4 patients in the indomethacin group and 7 patients in the placebo group (p=0.72). Two cases of acute renal failure occurred, both in the placebo group. While confirmatory data would be of interest, indomethacin appears to be the first unequivocally effective pharmacologic agent in the prevention of PEP in high-risk patients. Indeed, anecdotal data currently suggest that indomethacin is being increasingly adopted into widespread clinical use for the prophylaxis of PEP.

While the beneficial effect of indomethacin as demonstrated by Elmunzer et al. (17) represents a major advancement in PEP prevention, pancreatitis rates remain unacceptably high in high-risk patients -- nearly 10% in this study which took place in academic centers with experienced endoscopists. When used as an analgesic or anti-inflammatory agent in the management of patients with arthritis (gout, rheumatoid, ankylosing spondylitis), the recommended maximal daily dose of indomethacin is 200 mg per day, in divided doses (product insert, Merck & Co.). The half-life of this agent is approximately 4.5 hours. Potentially, a higher dose of indomethacin, perhaps leading to a higher peak serum concentration, might further lower PEP rates in high-risk patients. Alternatively, a second dose of the drug might lead to a more sustained effect. We acknowledge that there are no pharmacokinetic data to confirm or substantiate these hypotheses. If either of these phenomena is important in pancreatitis prevention, then a regimen consisting of a higher initial dose followed by a second dose may be hypothesized to be superior.

While all patients undergoing ERCP may benefit from the protective effect of indomethacin, the incidence of pancreatitis in high-risk patients is such that prevention of PEP in this patient population would lead to the most substantial reduction in morbidity and health care costs. Moreover, the elevated baseline risk of PEP in high-risk patients makes clinical trials in this group more feasible due to more manageable sample sizes.

Our objective is to perform a prospective, randomized, double-blind trial evaluating two different dose regimens of rectal indomethacin in the prevention of PEP. While a single 100 mg dose (the “standard” dose) is effective in high-risk patients (17), the ideal or most efficacious dose regimen is unknown. This study will determine which dose regimen of rectal indomethacin is more effective in preventing post-ERCP pancreatitis. The results will help the research team determine whether there is reason to continue this line of research or whether it would be better to focus on a different area (perhaps use of another class of drugs or a device).

D. Sample size calculation:

An internal audit of high-risk ERCPs at the four tertiary referral centers involved in this clinical trial reveals a PEP rate of approximately 10%, despite the routine use of prophylactic pancreatic duct stent placement (24-26) in appropriate patients and selective use of indomethacin. It is anticipated that the patient characteristics/demographics in this study will be very similar to that of Elmunzer et al. (17), as inclusion and exclusion criteria will be the same (see below). In that study (17), the PEP rate in patients who received indomethacin 100 mg was 9.2%. To achieve a 50% reduction in the rate of PEP (i.e. to 4.6%), with two-sided $\alpha=0.05$ and a power of 0.8, the necessary sample size is 1036. This absolute reduction in incidence

is felt to be clinically relevant and substantial enough to change existing clinical practice.

E. Methodology- Design and procedures

This study is designed as a prospective, randomized, double-blind clinical trial. We plan on enrolling 1036 high-risk patients undergoing ERCP. These patients will be enrolled at six tertiary care hospitals in the United States: Indiana University Hospital (Indianapolis, IN), University of Michigan Medical Center (Ann Arbor, MI), Methodist Dallas Medical Center (Dallas, TX), Aurora St. Luke's Medical Center (Milwaukee, WI), the Medical University of South Carolina (Charleston, SC), and Beth Israel Deaconess Medical Center (Boston, MA). The study will be conducted after approval from the internal review committees of all participating institutions. We have been granted an IND exemption from the Food and Drug Administration for this protocol (see attached).

Patients, study personnel, and treating physicians will be blinded to study group assignment. The randomization schedule, which is stratified according to study center, will be generated centrally at the University of Michigan and distributed to the other study sites. The randomization schedule will be kept by personnel not directly involved with the study. This same personnel will be responsible for packaging the drug and placebo. Based on current annual procedure volume, it is assumed that 700 patients will be recruited by the Indiana University site, with 336 patients recruited by the other sites. These estimates are not binding, as all sites will be allowed to continue recruiting patients until the recruitment goal is met, or interim analyses suggest early study termination. The individual sites will order the indomethacin suppositories as necessary through the research coordinator at Indiana University, as determined by their recruitment rate. The exception to this is MUSC will be ordering indomethacin suppositories on their own, which will come from the same manufacturer, G and W laboratories, that all other sites are using. The glycerin suppositories will be obtained either by each institution's standard ordering procedure, or by ordering from Indiana University. If ordering from Indiana University, the suppositories will be shipped directly to each individual site.

Inclusion criteria:

The inclusion criteria are intended to select a group of patients at high-risk (approximately 10%) for post-ERCP pancreatitis. These criteria are based on patient and procedure-related risk factors that have been previously shown in multivariable analyses to confer a significantly increased risk of PEP.

Included patients are those undergoing ERCP and have:

one of the following:

1) Suspected sphincter of Oddi dysfunction, type I or type II
2) History of post-ERCP pancreatitis (at least one episode)
3) Pancreatic sphincterotomy
4) Pre-cut (access) sphincterotomy
5) > 8 cannulation attempts of any sphincter
6) Pneumatic dilation of intact biliary sphincter
7) Ampullectomy
8) Assessment for post-sphincterotomy stenosis

or **at least 2** of the following:

1) Age < 50 years old and female gender
2) History of recurrent pancreatitis (at least 2 episodes)
3) ≥3 pancreatic injections, with at least one injection to tail
4) Pancreatic acinarization (excluding ventral pancreas of pancreas divisum)

5) Pancreatic brush cytology.

Exclusion criteria:
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1) Unwillingness or inability to consent for the study
2) Age < 18 years
3) Intrauterine pregnancy
4) Breastfeeding mother
5) Standard contraindications to ERCP
6) Allergy / hypersensitivity to aspirin or NSAIDs
7) Received NSAIDS in prior 7 days (aspirin 325 mg or less OK)
8) Renal failure (Cr > 1.4)
9) Active or recent (within 4 weeks) gastrointestinal hemorrhage
10) Acute pancreatitis (lipase peak) within 72 hours
11) Known chronic calcific pancreatitis
12) Pancreatic head mass
13) Procedure performed on major papilla/ventral pancreatic duct in a patient with pancreas divisum (dorsal duct not attempted or injected)
14) ERCP for biliary stent removal or exchange without anticipated pancreatogram
15) Subject with prior biliary sphincterotomy now scheduled for repeat biliary therapy without anticipated pancreatogram
16) Anticipated inability to follow protocol
17) Known active cardiovascular or cerebrovascular disease

Protocol:

Subjects who do not meet any exclusion criteria may be consented for the trial by a clinical research coordinator or one of the investigators. The consent process will occur prior to ERCP in the procedure preparation area. At this time, the objectives of the study as well as the risks and benefits of enrolling will be explained in detail to potential subjects.

After obtaining informed consent, subjects will undergo ERCP per clinical protocol. All procedure-related clinical decisions and interventions will be dictated by the performing physician as he or she sees fit. At the end of the procedure, it will be determined by the endoscopist and research coordinator whether the patient meets inclusion criteria. If inclusion criteria are met, subjects will be randomized by concealed allocation to receive either 100 mg or 150 mg indomethacin, in the form of two or three 50 mg identical-appearing rectal suppositories. Those patients who are randomized to receive the 100 mg dose will receive an additional glycerin suppository. The suppositories will be placed while the patient is still sedated in the ERCP suite, prior to transfer to the recovery area. Four hours later (+/- 20 minutes), those patients who were randomized to the high-dose group (already received 150 mg dose) will then receive an additional 50 mg suppository while in the recovery area. At this same time point, subjects who were randomized to the standard-dose group (already received 100 mg dose) will receive a glycerin suppository in the recovery area. All participating patients, therefore, will receive a total of 4 suppositories, as summarized below:

	Immediately post-ERCP	***4 hours post-ERCP***
High dose	Indomethacin 150 mg (50 mg x 3)	Indomethacin 50 mg x 1
Standard dose	Indomethacin 100 mg (50 mg x 2) + glycerin x1	glycerin x 1

There will be one source of indomethacin suppositories for all six participating sites. G and W Laboratories, Inc., South Plainfield, NJ 07080 will manufacture the indomethacin suppositories. The suppositories will then be distributed by IROKO Pharmaceuticals, LLC, Philadelphia, PA 19112.

Indomethacin and glycerin suppositories will be packaged according to the randomization schedule by personnel not directly involved in the conduct or interpretation of the study. The study package for each subject will be an opaque envelope or bottle. High-dose packages will contain 2 small plastic bags: bag #1 containing 3 indomethacin suppositories and bag #2 containing 1 indomethacin suppository. Standard dose packages will contain 2 small plastic bags: bag #1 containing 2 indomethacin suppositories and 1 glycerin suppository and bag #2 containing 1 glycerin suppository. The package will be fully opaque such that the contents of cannot be discerned without opening the envelope or bottle.

Since there are differences in the appearance of the indomethacin and glycerin suppositories, they will only be administered by clinical nurses not involved in the study. Immediately after ERCP, the clinical nurse will be instructed to deliver contents of bag #1 and the sealed package will be returned to the study coordinator, who will instruct a clinical nurse to deliver the contents of bag #2 approximately four hours after the procedure.

The packages will be stored in a clinical refrigerator prior to administration of bag #1 and between administration of bags #1 and #2.

Pancreatic duct stent placement will be at the discretion of the endoscopist on a case-by-case basis, as patients enrolled in this study will be considered to be at high-risk for PEP. The manufacturer, length, and caliber of prophylactic pancreatic stents will also be left to the discretion of the endoscopist, reflecting the variability in clinical practices in this area.

At our institutions, subjects are observed in the recovery area for approximately 4 hours after the termination of the procedure. Patients who develop abdominal pain (or worsening of their baseline abdominal pain) during this observation period are generally admitted to the hospital (for current inpatients, kept in the hospital) in order to exclude procedural complications, including pancreatitis and perforation. The decision to admit the patient or prolong existing hospitalization will be left to the discretion of the endoscopist and clinical service, respectively. Those patients who are hospitalized will have serum amylase and lipase drawn at least once 24 hours after the procedure and subsequently at the discretion of the clinical service. Patients who are discharged uneventfully after ERCP will be contacted by telephone or email within 5 ± 2 days of the procedure by a study team member to evaluate for the development of post-ERCP pancreatitis and other related or unrelated complications. All subjects will also be contacted 30 ± 5 days by telephone or email after the procedure to verify that information about complications has been captured, particularly bleeding which can be delayed after ERCP. Definitions: PEP will be defined per consensus guidelines (27): 1) New or increased abdominal pain that is clinically consistent with a syndrome of acute pancreatitis **and** 2) amylase or lipase ≥ 3x the upper limit of normal 24 hours after the procedure **and** 3) Hospitalization (or prolongation of existing hospitalization) for at least 2 days (at least night of ERCP & next night). Mild PEP will be defined as pancreatitis that results in hospitalization (or prolongation of existing hospitalization) for ≤3 days. Moderate PEP will be defined as pancreatitis that results in hospitalization (or prolongation of existing hospitalization) for 4-10 days. Severe PEP will be defined as pancreatitis that results in hospitalization (or prolongation of existing hospitalization) for > 10 days, or leads to the development of pancreatic necrosis or pseudocyst, or requires additional endoscopic, percutaneous, or surgical intervention.

Data management:

Patient demographics, risk factors, the procedural elements of the ERCP, and follow-up data will be

recorded on a standardized data collection form at the time of the procedure and within 5 days and 30 days after the procedure. This information will be recorded by a research coordinator. All completed data collection forms from the University of Michigan Medical Center, Methodist Dallas Medical Center, Aurora St. Luke's Medical Center,the Medical University of South Carolina, and Beth Israel Deaconess Medical Center will be faxed, emailed, or uploaded into MiShare and sent to IU. The data will be transferred by the IU study coordinator to a master excel database, housed on a password protected desktop computer in a locked research office. A second research team member from IU will perform data entry confirmation.

F. Statistical analysis

For the analysis of the primary endpoint, the difference in the proportion of patients developing post-ERCP pancreatitis between the two groups will be analyzed using a two-tailed Fisher's exact test, with a two-sided $p < 0.05$ indicating statistical significance.

After enrolling 400 patients (37.7% of total enrollment) a BLINDED interim analysis will be conducted by the independent DSMB as follows. For each subject the DSMB will be provided with 1) the subject ID number, 2) whether or not the primary endpoint (post-ERCP pancreatitis) occurred, 3) whether or not a bleeding event occurred, and 4) in which group (high-dose or standard dose regimen) the patient belonged. If > 66% of the pancreatitis cases or bleeding cases are in a particular group (high-dose or standard dose regimen), the DSMB will break the code to determine whether these events are in the standard 100 mg indomethacin group or high-dose indomethacin group. This value was selected because it represents a 2:1 (double) frequency of an endpoint outcome in one group or another. If either of these events has occurred at this high frequency in one group or another, then the DSMB will decide that the study should be stopped. Even if the DSMB is required to break the code for this above listed purpose, the investigators will never be aware of this information. The DSMB will simply tell the investigators whether or not to continue the study. If during this blinded interim analysis, the DSMB finds that the proportion of the patients with pancreatitis in the higher dose indomethacin group is significantly lower, a formal statistical analysis will be performed and statistical significance will only be declared (and the study terminated) if the two-sided p value is less than 0.005. In this unlikely circumstance, the DSMB will inform the investigators that the study should be terminated for ethical reasons (i.e., it would be unethical to withhold this from high-risk patients).

After enrolling 600 subjects (56.6% of total enrollment) a BLINDED interim analysis will be conducted by the independent DSMB as follows. For each subject the DSMB will be provided with 1) the subject ID number, 2) whether or not the primary endpoint (post-ERCP pancreatitis) occurred, 3) whether or not a bleeding event occurred, and 4) in which group (high-dose or standard dose regimen) the patient belonged. This analysis will be performed because it was a specific request of the DSMB that it be performed to ensure the safety of subjects. Analysis and criteria for stopping the study at this second interim analysis will be the same as those noted above, for the first interim analysis.

For the analysis of the secondary endpoint, the difference in the proportion of patients developing moderate-severe PEP between the two groups will be analyzed using a two-tailed Fisher's exact test.

An additional secondary analysis will include the multivariate evaluation of the prediction of PEP by treatment arm while controlling for covariates, which we expect may contribute to the variance in PEP incidence. These covariates will include:

Clinical suspicion of sphincter of Oddi dysfunction
Age
Gender
Race
Body mass index
History of recurrent pancreatitis (at least 2 episodes)
History of post-ERCP pancreatitis (at least one episode)

Pancreatic sphincterotomy
Pre-cut (access) sphincterotomy
Number of cannulation attempts
Number of pancreatic injections
Pneumatic dilation of intact biliary sphincter
Ampullectomy
Pancreatic brush cytology
Pancreatic acinarization
Cardioprotective aspirin use
Pancreatic duct stent placement
Use of double wire cannulation technique
Trainee involvement in procedure
Biliary sphincterotomy
Prophylactic pancreatic stent characteristics (manufacturer/length/caliber)
Type of sphincter of Oddi dysfunction (suspicion, pre-manometry)
Inpatient vs. outpatient status
Participating medical center

We realize that the event rate may be too low to include more than a few variables in the multivariate model. Based on univariate analysis of each variable in predicting PEP, we will include no more than one variable per 10 PEP events in the final multivariate model predicting PEP.

Exploratory subgroup analyses will also be performed on the following pre-specified characteristics: age, gender, race, body mass index, suspicion of sphincter of Oddi dysfunction, prior post-ERCP pancreatitis, history of recurrent pancreatitis, manometrically documented sphincter of Oddi dysfunction, difficult cannulation, pre-cut (access) sphincterotomy, pancreatic sphincterotomy, pancreatic acinarization, biliary sphincterotomy, double wire cannulation technique pancreatic stent placement, trainee involvement, cardioprotective aspirin use, prophylactic pancreatic stent characteristics, type of sphincter of Oddi dysfunction, inpatient vs. outpatient status, and participating medical center. These subgroup analyses will allow the development of hypotheses regarding which subgroups of patients, if any, may particularly benefit from a more intensive indomethacin regimen.

Further, we will perform a heterogeneity in treatment effects analysis on enrolled subjects according to their pre-treatment risk of post-ERCP pancreatitis, functionally assessing whether the relative treatment effect is consistent across the spectrum of study subjects' risk of post-ERCP pancreatitis. Individual subject risk scores will be calculated by assigning one point for each major inclusion criterion and 0.5 points for each minor inclusion criterion, as previously reported (17).

It is recognized that some patients may have difficulty holding their suppositories, and expulsion of the suppositories may or may not be witnessed by study personnel. All patients will be analyzed on an intent-to-treat basis, in the group to which they were randomized. However, we anticipate that this point will have little impact on study outcome, as indomethacin suppositories dissolve quickly (rather than melt slowly) and are seldom recovered in recognizable form if the patient retains the suppository for more than a few minutes (product insert, Merck & Co.). If a suppository is recovered in visible and intact form, it may be re-inserted.

G. Budget

Funding for this study has been obtained from the American College of Gastroenterology. The Clinical Research Award amount is $34,975 which will be used for medication costs for all sites, as well as coordinator support at Indiana University.

References:

1. La Ferla G, Gordon S, Archibald M, et al. Hyperamylasaemia and acute pancreatitis following endoscopic retrograde cholangiopancreatography. Pancreas 1986;1(2):160-163.

2. Sherman S, Lehman GA. ERCP and endoscopic sphincterotomy-induced pancreatitis. Pancreas 1991;6:350-67.

3. Freeman ML, Nelson DB, Sherman S, et al. Complications of endoscopic biliary sphincterotomy. N Engl J Med 1996;335:909-18.

4. Frank CD, Adler DG. Post-ERCP pancreatitis and its prevention. Nat Clin Pract Gastroenterol Hepatol. 2006;3:680-8

5. Gross V, Leser HG, Heinisch A, at al. Inflammatory mediators and cytokines-new aspects of the pathophysiology and assessment of severity of acute pancreatitis? Hepatogastroenterol 1993;40:522-530.

6. Makela A, Kuusi T, Schroeder T. Inhibition of serum phospholipase A2 in acute pancreatitis by pharamacologic agents in vitro. Scand J Clin Lab Invest 1997;57:401-408.

7. Davies NM, Anderson KE. Clinical phamacokinetics of diclofenac. Therapeutic insights and pitfalls. Clin Pharamakokinet 1997; 33:184-213.

8. Lankisch PG, Koop H, Winckler K et al. Indomethacin treatment of acute experimental pancreatitis in the rat. Scand J Gastroenterol 1978;13:629-633.

9. Wildenhain PM, Melhem MF, Birsic WI, et al. Acute hemorrhagic pancreatitis in mice: improved survival after indomethacin administration. Digestion 1989;44:41-51.

10. Cosen-Binker LI, Binker MG, Cosen R, et al. Influence of nitric oxide-donating nonsteroidal anti-inflammatory drugs on the evolution of acute pancreatitis. Shock 2006;25:190-203.

11. Ebbehøj N, Friis J, Svendsen LB, et al. Indomethacin treatment of acute pancreatitis. A controlled double-blind trial. Scand J Gastroenterol 1985;20:798-800.

12. Murray B, Carter R, Imrie C, et al. Diclofenac reduces the incidence of acute pancreatitis after endoscopic retrograde cholangiopancreatography. Gastroenterology 2003;124:1786-1791.

13. Sotousdehmanesh R, Khatibian M, Kolahdoozan S, et al. Indomethacin may reduce the incidence and severity of acute pancreatitis after ERCP. Am J Gastroenterol 2007; 102:978-983.

14. Khoshbaten M, Khorram H, Mamad L, et al. Role of diclofenac in reducing postendoscopic retrograde cholangiopancreatography pancreatitis. J Gastroenetrol Hepatol 2007; epub ahead of print.

15. Montaño Loza A, Rodriguez Lomeli X, Garcia Correa J, et al. Effect of rectal administration of indomethacin on amylase serum levels after endoscopic retrograde cholangiopancreatography, and its impact on the development of secondary pancreatitis episodes. Rev Esp Enferm Dig 2007;99:330-336.

16. Cheon Y, Cho K, Watkins J, et al. Efficacy of diclofenac in the prevention of post- ERCP pancreatitis in predominantly high risk patients: a randomized double-blind prospective trial. Gastrointest Endosc 2007;66:1126-1132.

17. Elmunzer BJ, Scheiman JM, Lehman GA, et al. A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. N Engl J Med 2012;366:1414-22.

18. Nelson DB, Freeman ML. Major hemorrhage from endoscopic sphincterotomy: risk factor analysis. J Clin Gastroenterol 1994;19:283-287.

19. Elmunzer B, Waljee A, Elta G, et al. A meta-analysis of rectal NSAIDs in the prevention of post-ERCP pancreatitis. Gut 2008; epub ahead of print.

20. Van Der Marel C, Anderson BJ, Romsing J, et al. Diclofenac and metabolite pharmacokinetics in children. Paediatr Anesth 2004;14:443-451.

21. Gross V, Leser HG, Heinisch A, at al. Inflammatory mediators and cytokines - new aspects of pathophysiology and assessment of severity of acute pancreatitis? Hepatogastroenterol 1993;40:522-530.

22. Andriulli A, Leandro G, Niro G, et al. Pharmacologic treatment can prevent pancreatic injury after ERCP: a meta-analysis. Gastrointest Endosc 2000;51:1-7.

23. Andriulli A, Leandro G, Federici T, at al. Prophylactic administration of somatostatin or gabexate does not prevent pancreatitis after ERCP: an updated meta-analysis. Gastrointest Endosc 2007;65: 624-632.

24. Tarnasky P, Palesch Y, Cunningham JT, et al. Pancreatic stenting prevents pancreatitis after biliary sphincterotomy in patients with sphincter of Oddi dysfunction. Gastroenterology 1998;115:1518-24.

25. Fazel A, Quadri A, Catalano MF, et al. Does a pancreatic duct stent prevent post-ERCP pancreatitis? A prospective randomized study. Gastrointest Endosc 2003;57:291-4.

26. Singh P, Das A, Isenberg G, et al. Does prophylactic pancreatic stent placement reduce the risk of post-ERCP pancreatitis? A meta-analysis of controlled trials. Gastrointest Endosc 2004; 60: 544-550.

27. Cotton PB, Lehman G, Vennes J, et al. Endoscopic sphincterotomy complications and their management: an attempt at consensus. Gastrointest Endosc 1991;37:383-393.