REVIEW ARTICLE

The Role of Nonsteroidal Anti-inflammatory Drugs in the Prevention of Post Endoscopic Retrograde Cholangiopancreatography Pancreatitis

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ABSTRACT

Post-ERCP pancreatitis (PEP) is the most common major complication associated with ERCP. Beginning with an overview of the risk factors for the development of PEP, this review introduces the mechanism of injury in PEP and the role of pharmacological prevention. NSAIDs are increasingly found to offer prevention against the development of PEP, and their mechanism and supportive data are summarized, especially in relationship to the practice of prophylactic pancreatic duct stenting.

INTRODUCTION

Post-ERCP pancreatitis (PEP) is the most common major complication associated with ERCP [1]. It is distinct from asymptomatic hyperenzymemia [2] and may present with varying levels of severity, which influence inpatient length of stay and prognosis [3]. Multiple risk factors for the development of PEP have been identified and are broadly categorized into patient-dependent or procedure-dependent risks. The patient dependent risks most consistently identified are female gender, younger age, suspected sphincter of Oddi dysfunction (SOD) as an indication, previous episodes of PEP, current alcohol use, former cigarette smoking, lack of chronic pancreatitis and the presence of normal serum bilirubin. Procedure and operator dependent risk factors include difficult cannulation, pancreatic duct (PD) contrast injection (the risk of PEP increasing proportionally with number of injections), use of precut or access sphincterotomy, PD sphincterotomy, minor papilla sphincterotomy, failed clearance and operator inadequacy [1, 3-11].

The primary role of pharmacologic prevention of post-ERCP pancreatitis is to reduce the levels of intra-pancreatic enzymes and prevent the activation of digestive enzymes and lysosomal hydrolases. Over 35 different drugs have been studied to date. Chemopreventive studies have targeted various mechanisms of injury including protease inhibitors (gabexate and ulinastatin), modulators of pancreatic enzyme secretion (octreotide and somatostatin), smooth muscle relaxants (nitroglycerin, phosphodiesterase inhibitors and calcium channel blockers), and anti-inflammatories (NSAIDs, corticosteroids, IL-10 and heparin). While pharmacologic prophylaxis has been appealing, many drugs have failed to show significant reduction in PEP and the prophylactic placement of PD stents has gained widespread acceptance [12-14]. The technique, however, is demanding even in experienced hands and carries costs and potentially serious adverse outcomes [15]. The administration of NSAIDs however, is generally safe, straightforward and inexpensive. Thus investigative efforts into their chemopreventive roles in PEP has emerged over the last decade.

NSAID MECHANISM OF ACTION

The pathophysiology of PEP involves various inciting events that lead to a common final pathway of inappropriate activation of pancreatic enzymes and auto-digestion. These inciting events may cause mechanical obstruction (from trauma or edema of the pancreatic sphincter or duct), may increase pancreatic ductal pressure or may be functional due to spasm of the sphincter of Oddi [16]. Infection from instrumentation, duodenal contents or increased hydrostatic pressure may also be inciting events, the latter possibly resulting from overinjection of contrast medium and subsequent damage to ductal epithelial cells [9, 16]. While conflicting evidence regarding the role of acinarization have been observed, the use of ionic contrast medium has not been found to be a significant risk factor [3, 9, 17-20]. Repeated attempts at cannulation, however, do increase the risk of developing PEP [14].

While risk factors predispose certain patients to developing PEP, there have been several steps described that take place after the inciting event which lead to a common pathophysiology of acute pancreatitis [21, 22]. After trypsinogen activation, a local inflammatory response is triggered by acinar cell damage [23] and numerous inflammatory mediators are implicated in this process, several of which are relevant to the discussion of NSAIDs and their action in PEP. The 4 main mechanisms by which NSAIDs act are: inhibition of cylcooxygenase (COX), inhibition of phospholipase A2 (PLA), prevention of leukocyte adhesion and migration, and inhibition of integrins.

The most well described mechanism is the inhibition of the COX2 enzyme, which may or may not be selective. In an early paper, Vane described the decreased production of prostaglandins by aspirin and indomethacin administration [24]. COX2 is the enzyme responsible for catalyzing the rate limiting step of the conversion of arachidonic acid to prostaglandin and thromboxane, both of which are known to be important in acute inflammatory reactions [25]. In murine models of acute pancreatitis, COX2 mRNA is increased, in turn leading to increased production of prostaglandin [26]. There have also been studies on arachidonic acid metabolites in acute pancreatitis in porcine models. In these studies pancreatitis was induced by injection of free fatty acid and various arachidonic acid metabolites were measured. The prostaglandins PGF1 alpha and PGF2 alpha and thromboxane B2 were found to be elevated in lymph, and increased levels of PGF1 were found in pancreatic venous blood [27].

Additionally, several studies have been conducted in animal models involving administration of selective or non-selective COX inhibitors. Ethridge et al. induced pancreatitis in either COX1 or COX2 knockout mice or a wild-type followed by administration of NS-398 (a selective COX2 inhibitor). They surveyed the pancreas and lungs histologically and found less severe pancreatic injury in the COX2 knockout [28]. Similar results have been confirmed using either histologic or biochemical markers of pancreatitis severity and have suggested a role of COX2 metabolites in not only local but systemic inflammation with COX2 inhibition leading to attenuated lung and renal injury [29-31].

Phospholipase A2 [PLA2] is an enzyme that catalyzes the lipolysis of phosphoglycerides at the sn-2 position and leads to the release of arachidonic acid [32]. Two different types have been described in the context of acute pancreatitis. Type II phospholipase A2 has been demonstrated to have a substantially increased activity in murine models of acute pancreatitis, particularly in necrotizing and severe variants associated with lung injury [33, 34]. The association of increased PLA2 activity with pancreatitis has also been investigated in human studies that reveal an association of increased catalytic activity of PLA2 with necrotizing pancreatitis and pancreatitis complicated by respiratory dysfunction [35, 36]. Interestingly, indomethacin has been demonstrated to reduce PLA2 activity in vitro in a study that used serum from patients with necrotizing pancreatitis as an enzymatic source [37]. The study found that indomethacin exhibited the strongest inhibition of PLA2 of all agents tested (diclofenac, ketoprofen, chlorpromazine, tobramycin, doxycycline, several coritcosteroids, bupivacaine, digoxin, lidocaine, metoprolol, and vancomycin). Of note, diclofenac did reduce PLA2 activity by 93% but at supratherapeutic administration [37].

The neutrophil adhesion and extravasation process presents another mechanism on which NSAIDs may act to ameliorate acute pancreatitis. After an appropriate stimulation from pro-inflammatory cytokines, endothelial cells and neutrophils begin the "rolling" process whereby they interact and bind with one another [38]. The end result of this process is migration of the activated neutrophil from the lumen of the capillary to the extracellular space. Further studies have suggested that NSAIDs modulate this process by exerting a dose and time dependent down-regulation on the L-selectin molecule present on the neutrophil surface [39, 40], and are important in facilitating neutrophil-endothelial cell adhesion [38].

NSAIDs are also able to interfere with the activation process of integrins important in platelet activation. The glycoprotein IIb/IIIa (αIIbβ3) integrin is an important integrin responsible for platelet aggregation and adhesion via its binding of platelets to von Willebrand factor, fibrinogen, vitronectin, fibronectin, and collegen [41]. Meloxicam, piroxicam, indomethacin and aspirin, but not aceclofenac or diclofenac, decreased integrin αIIbβ3 ativation independent of their inhibition of COX [42]. Additionally, piroxicam and meloxicam have been shown to exert several different effects on integrins in neutrophil activation. Both drugs prevent L-selectin and CD11b activation, a process important in neutrophil activation and induced by TNF and other inflammatory molecules [43]. The same study also showed that piroxicam treatment prevented changes in the beta 1 integrins important in the activation of T lymphocytes [43]. Furthermore, salicylates have also been shown to decrease T lymphocyte migration via mitigation of an integrin-mediated mechanism [44].

CLINICAL STUDIES

Initial studies evaluating the role of NSAID's demonstrated the efficacy of oral or intramuscular administration in reducing mortality in rodents [45]. Moreover, in a double blind controlled study, Danish researchers used indomethacin 50mg twice daily rectal suppositories to demonstrate a significant reduction in the frequency and intensity of acute pancreatitis [46]. NSAIDs are inexpensive, simple to administer and relatively safe. While their application in pancreatitis is not new, their investigation for chemoprevention in PEP has been a natural progression over the last decade.

In the first randomized controlled trial (RCT), Murray et al. demonstrated the efficacy of rectal diclofenac administration immediately after ERCP to prevent PEP. A total of 220 patients were evaluated with 110

receiving rectal diclofenac and the others a placebo. PEP was reduced in the diclofenac group compared to those receiving placebo (6.4% vs. 15.5%, p=0.049) [47]. While the study only marginally achieved statistical significance, interestingly it showed no benefit in the highest risk population, patients with SOD; and was further limited by the lack of multivariate analysis.

Subsequent trials evaluating the efficacy of NSAID's yielded dichotomous results (Table 1) [47-54]. While there was a trend towards a lower incidence of PEP, the studies were complicated by differing designs and definitions of PEP; raising further questions regarding the role of NSAID prophylaxis. In a meta-analysis of four studies involving rectally administered NSAID's (a total of 912 patients), Elmunzer et al. sought to provide clarity to this issue. The analysis revealed a pooled relative risk for PEP of 0.36 (95%CI 0.22-0.60) after administration of prophylactic NSAIDs and a relative risk of 0.30 (95%CI 0.01-0.76) for moderate to severe pancreatitis [55]. Rectally administered NSAID's distinctly demonstrated a tendency toward the reduction of incidence and severity of PEP. Congruent with these findings, another meta-analysis involving 6 randomized controlled trials with a total of 1,300 patients (treatment arm included both rectal diclofenac and oral indomethacin) found a statistically significantly lower risk of PEP in the NSAID vs placebo arm [56]. Authors of both meta-analyses concluded that while NSAIDs appeared to be effective in preventing PEP, there were several limitations including the small number of trials and sample size, inconsistent definitions of PEP (two trials used serum amylase levels of 4 times the upper limit of normal), and restrictive representative populations for which widespread applicability was uncertain.

After the publication of these meta-analyses, three more trials provided further conflicting results regarding NSAID chemoprophylaxis [53, 57, 58]. While one trial had positive findings [53], two others demonstrated no benefit [57, 58]. Given the inconsistent data, rectal NSAID's were infrequently used in practice. Furthermore, despite the evidence from animal trials (discussed above) suggesting the efficacy of selective COX2 inhibitors in acute pancreatitis, a human study of valdecoxib in the prevention of PEP showed no significant effect [59]. In fact, several case reports implicating selective COX2 inhibitors as an etiology of acute pancreatitis were described [60-63].

More recently however, a large multicenter prospective randomized double blind placebo controlled trial was conducted in which patients undergoing ERCP (n=602) were randomized to receive 100mg indomethacin rectally (n=295) immediately after ERCP or placebo (n=307), with PEP rates of 27/295 (9.2%) vs 52/307 (16.9%); respectively, p=0.005 and moderate to severe PEP of 4.5% vs. 8.8%; respectively, p=0.03 [54]. The majority of patients included in the study were high risk, with clinical suspicion of SOD, suggesting that the results are applicable to this patient population. While this was the first large multicenter trial to demonstrate that a single dose of rectally administered indomethacin provided immediately after ERCP reduced the risk of PEP, especially in the highest risk patient population, it may have underemphasized the role of concomitant prophylactic stenting of the PD [64].

Similar to the two previous meta-analyses, a larger meta-analysis of 10 RCTs [47-51, 53, 54, 57-59] involving a total of 2,269 patients demonstrated a relative risk of PEP of 0.57 (95% CI, 0.38-0.86) after NSAID prophylaxis

Table 1. Analysis of Rectally Administered NSAID's for PEP.

Study[a]	Country/Setting	Year	Rectal NSAID Dose/Administration	Sample Size NSAID/Placebo	PD Stent Placement NSAID/ Placebo	Rate of PEP NSAID vs Placebo
Murray et al	Scotland/Single Center	2003	100mg Diclofenac immediately after ERCP	110/110	13/12	7/110 (6.3%) vs 17/110 (15%) d,g,h
Sotoudehmanesh et al	Iran/Single Center	2007	100mg Indomethacin immediately before ERCP	221/221	None	7/221 (3.2%) vs 15/221 (6.8%)c,e,i
Khoshbaten et al	Iran/Single Center	2007	100mg Diclofenac immediately after ERCP	50/50	None	2/50 (4%) vs 13/50 (26%)d,g,h
Cheon et al	United States/ Single Center	2007	50mg Diclofenac 30-90 minutes before ERCP and 4-6 hours after ERCP	105/102	71/73	17/105 (16.2%) vs 17/102 (16.7%)d,e,i
Montano Lazo et al	Mexico/Multi-center	2007	100mg Indomethacin 2 hours before ERCP	75/75	10/9	4/75 (5%) vs 12/75 (6.8%)c,f,i
Katsinelos et al	Greece/Multi-center	2011	100mg Diclofenac 30-60 minutes before ERCP with 0.25mg/hour Somatostatin for 6 hours	255/260	None	12/255 (5%) vs 27/260 (10%)c,e
Otsuka et al	Japan/Multi-center	2012	50mg Diclofenac 30 minutes before ERCPb	51/53	None	2/51 (4%) vs 10/53 (19%)c,e,i
Elmunzer et al	United States/ Multicenter	2012	100mg Indomethacin immediately after ERCP	295/307	246/250	27/295 (9%) vs 52/307 (17%) c,e,h

[a]All randomized control trials; b25 mg used if body weight < 50 kg; cPEP defined by Cotton criteria [68]; dPEP defined by serum amylase level > 3-4 times the normal level with associated abdominal pain; eSeverity of pancreatitis determined by Cotton criteria; fSeverity of pancreatitis determined by Ranson criteria; gNo specified definition of the severity of pancreatitis; hOnly patients undergoing high risk ERCP; iIncluded all patients undergoing ERCP

[65]. In this analysis, patients receiving NSAID's were 43% less likely to experience PEP. The analysis further demonstrated a 54% reduction in the development of moderate to severe PEP. Moreover, peri-procedural NSAID use revealed no significant adverse events, thereby highlighting their relative safety at 1 or 2 doses. The meta-analysis; however, had limitations. Three low-quality trials [50, 53, 57] were included which are susceptible to bias, rending their results questionable. Further, three different kinds of NSAID's were utilized in the included trials (diclofenac, indomethacin, and valdecoxib), with varying routes of administration and doses. Interestingly, the six studies assessing rectally administered NSAIDs were positive; whereas the four studies [51, 57-59] using oral, intravenous, intramuscular, and intraduodenal NSAIDs yielded negative results. Based on the limited studies, it would seem that rectally administered NSAIDs are the most effective for chemoprophylaxis. However, further studies are required to assess whether the route of administration plays a role in the prevention of post-procedure pancreatitis.

While rectal NSAID's remain a convenient and effective therapy, the timing of NSAID administration remains a question. Previous clinic trials assessing the role for NSAID prophylaxis has included both pre-ERCP and post-ERCP drug administration [47-54, 60]. In a meta-analysis by Sethi et al. the timing of NSAID's (pre vs post) demonstrated no difference in the efficacy of preventing PEP [66]. Post-ERCP administration appears to be the most logical; thereby, limiting unnecessary drug administration and targeting NSAID's for higher risk patients.

A ROLE FOR NSAIDS VIS-A-VIS PD STENTING

Over the last decade, the use of temporary PD stenting and now NSAIDs have been shown to be effective for PEP prophylaxis. The most significant limitation in prior studies in assessing the true effect of NSAID prophylaxis has been the inability to accurately identify the rate of prophylactic pancreatic stents usage in the study populations. In their multicenter randomized trial, Elmunzer et al. identified that more than 80% of patients had PD stent placement in addition to indomethacin or placebo. Indomethacin conferred a similar reduction in the risk of PEP in both patients with and without PD stent placement: 16.1% vs 9.7% (p=0.04) and 20.6% vs 6.3% (p=0.049), respectively [54]. This established the efficacy of NSAIDs for chemoprophylaxis in high-risk patients requiring PD stenting. PD stent placement remains technically demanding and costly, while the administration of NSAIDs is cost-effective and safe; making it an attractive alternative. A recent network meta-analysis performed both direct and indirect comparisons of rectal NSAIDs and PD stents to assess for the reduction of PEP [67]. The results demonstrated no significant benefit of rectal NSAIDs plus stents compared to NSAIDs alone (OR, 1.46; 95% CI, 0.79-2.69). When rectal NSAIDs were compared to stents, the pooled analysis was positive for NSAIDs (OR, 0.48; 95% CI, 0.26 -0.87). The clinical implications of these findings are significant and suggest that NSAIDs may offer a primary alternative to PD stent placement, especially in high-risk patients. However, given the limited number of studies involving high-risk patients and the inherent limitation of extrapolation in network meta-analysis, further randomized prospective trials are required to draw this conclusion confidently.

CONCLUSION

While prior attempts at pharmacologic prevention of post-ERCP pancreatitis have been disappointing, NSAIDs remain inexpensive, simple and safe to use. Given the most recent prospective multicenter trial and network meta-analysis demonstrating the efficacy of rectal indomethacin, the prophylactic administration of a single dose rectal NSAID will likely gain wider acceptance. Until then, further high quality RCTs are needed to better compare prophylactic rectal NSAIDs versus prophylactic PD stenting in average and high-risk patients.

Conflict of Interest

The authors did not report any potential conflicts of interest.

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