KJIM

Can postendoscopic retrograde cholangiopancreatography pancreatitis be prevented by a pharmacological approach?

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Acute pancreatitis remains the most frequent complication of endoscopic retrograde cholangiopancreatography (ERCP), with reported incidence rates that have changed little over several decades. Patient- and procedure-related risk factors for post-ERCP pancreatitis (PEP) are well-defined. Effective measures to prevent PEP have been identified, including improvements in cannulation techniques and pancreatic stenting, as well as pharmacological intervention. Pharmacotherapy has been widely studied in the prevention of PEP, but the effect in averting PEP has been inconclusive. Although pharmacological prophylaxis is appealing, attempts to find an ideal drug are incomplete. Most available data on the efficacy of pharmacological agents for PEP prophylaxis have been obtained from patients at average risk for PEP. However, recently, a randomized prospective controlled trial of rectal nonsteroidal anti-inflammatory drugs (NSAIDs) to prevent PEP in high-risk patients was published. The results revealed that rectal indomethacin reduced the incidence of PEP significantly. Thus, rectal administration of diclofenac or indomethacin immediately before or after ERCP is used routinely to prevent PEP. However, additional studies with NSAIDs using large numbers of subjects are necessary to confirm the prophylactic effect of these drugs and to establish whether they act synergistically with other prophylactic interventions, including pancreatic stenting.

Keywords: Pancreatitis; Cholangiopancreatography, endoscopic retrograde; Anti-inflammatory agents, non-steroidal; Prevention and control

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is now widely accepted as a therapeutic modality; its application, however, is limited because of the technical difficulty and unavoidable incidence of complications. Complications of ERCP include pancreatitis, bleeding, cholangitis, cholecystitis, and perforation; of these, post-ERCP pancreatitis (PEP) is the most frequent. Rates of pancreatitis of 2% to 9% are typical of most unselected prospective series [1-3]. The risk of PEP varies greatly with indication, being < 5% for the management of common bile duct stones and reaching 20% or more in cases of suspected sphincter of Oddi dysfunction (SOD) [4]. Despite attempts to address this problem, effective strategies to prevent this serious complication remain elusive.

Patient- and procedure-related risk factors for PEP are well-known. Recently, effective measures to prevent PEP have been identified, including improvements in

cannulation techniques and pancreatic stenting, as well as pharmacological interventions.

Pharmacotherapy has been widely studied in the prevention of PEP, but the effects in averting PEP have been inconclusive. Although pharmacological prophylaxis is appealing, attempts to find an ideal drug are incomplete. Initial single-center randomized trials suggested efficacy, but were followed by conflicting results from larger multicenter studies [5].

Recently, a randomized prospective controlled trial (RCT) of rectal nonsteroidal anti-inflammatory drugs (NSAIDs) to prevent PEP in high-risk patients was published [6]. The results revealed that rectal indomethacin reduced the incidence of PEP significantly. If prophylaxis with an inexpensive drug and peri-procedural administration could decrease the incidence of PEP, it would translate into major medical and economic benefits. This review assesses the mechanisms and various results of pharmacotherapy to minimize the incidence and severity of PEP.

DEFINITION

A consensus classification was published in 1991 and defined this complication as a clinical syndrome, consistent with acute pancreatitis, with a serum amylase level at least three times normal at more than 24 hours after the procedure and requiring hospital admission or prolongation of a planned admission [7]. The severity of PEP is based primarily on the length of hospitalization: mild PEP is defined as the need for hospital admission or prolongation of planned admission up to 3 days, moderate PEP is defined by the need for hospitalization from 3 up to 10 days, and severe PEP by hospitalization for more than 10 days, or significant complications. It should be noted, however, that transient hyperamylasemia without acute pancreatitis is common after ERCP. If after 24 hours there is doubt about the diagnosis of acute pancreatitis, a contrast-enhanced abdominal computed tomography scan is advisable.

MECHANISMS OF PEP

Understanding the pathogenesis of PEP is important in its prevention. Many mechanisms have been suggested for the induction of PEP, but they can be categorized as follows [8]:

1) Mechanical obstruction: If the flow of pancreatic juice is obstructed by trauma to the pancreatic sphincter or proximal pancreatic duct, edema of the pancreatic sphincter secondary to sphincterotomy or thermal injury, or prolonged spasm of the pancreatic sphincter in patients with sphincter hypertension may result.
2) Hydrostatic pressure increase in the pancreatic duct: This may be related to the over injection of contrast medium, pancreatic manometry without aspiration, or an obstruction near the pancreatic sphincter (i.e., by compression from a distal bile duct stone).
3) Infection: The source of infection may be duodenal content, the endoscopic channel, or ERCP accessories.

Induction by whatever means leads to intrapancreatic digestive enzyme and cellular autodigestion. The patient's response to this insult is determined by the intensity of the inflammatory cascade and systemic response to this local event.

RESULTS OF PHARMACOLOGICAL APPROACHES TO PEP

A pharmacological agent that prevents PEP has been a goal of investigators for many years. The rationale for this effort centers on the interruption of one or more of the various postulated mechanisms of injury. Generally, chemopreventive studies have targeted five main areas:

1) The prevention of intra-acinar trypsinogen activation (gabexate and ulinastatin)
2) The reduction of pancreatic enzyme secretion (octreotide and somatostatin)
3) Relaxation of a sphincter of Oddi spasm (nitroglycerin [NG], phosphodiesterase [PDE] inhibitor type 5, and calcium channel blockers)
4) Interruption of the inflammatory cascade (NSAIDs,

corticosteroids, interleukin-10 [IL-10], and heparin)

5) The prevention of infection (antibiotics)

Although pharmacological prophylaxis is appealing, most available data have been obtained from patients at average risk for PEP. In such circumstances, insufficient statistical power might account for the lack of demonstrated drug efficacy [9]. Additionally, case mixes and/or the criteria used to define acute pancreatitis have varied [5]. These variations in design may explain some of the contrasting results with respect to the effectiveness of drugs between different studies.

Prevention of intra-acinar trypsinogen activation

Gabexate

The protease inhibitor gabexate is a diffusible, synthetic inhibitor of trypsin, kallikrein, and plasmin. When administered by continuous intravenous infusion, gabexate reaches a steady state within 15 minutes, with a half-life of 55 seconds [10], and is eliminated in its inactive form by the kidneys. In a RCT with 418 patients, an infusion of gabexate 30 to 90 minutes before ERCP and for 12 hours thereafter was associated with a significantly lower rate of pancreatitis (2.4%) compared with the control group (7.6%) [11]. An initial meta-analysis suggested that gabexate significantly reduced the risk of pancreatitis (odds ratio [OR], 0.27; 95% confidence interval [CI], 0.13 to 0.57); however, the number needed to prevent one episode of pancreatitis was relatively high, at 27 [12]. A subsequent large multicenter study of gabexate in a single dose before ERCP and continued for 2 hours thereafter found no significant difference in the frequency of pancreatitis in the treatment group (8.1%) versus the placebo group (6.5%) [13]. The schedule seemed unimportant, because neither a short duration of drug infusion (less than 6 hours) nor a long one (more than 12 hours) was beneficial [9].

Ulinastatin

Ulinastatin has been studied in four RCTs as an agent to prevent PEP. In two, it was compared with a placebo, and in two it was compared with gabexate. The results of these studies are contradictory [14-17]. In one RCT that included 406 patients [15], the incidence of PEP was significantly lower with ulinastatin (150,000 U ad-

ministered prior to ERCP) compared with the placebo (2.9% vs. 7.4%, p = 0.041). However, this benefit was not confirmed in another RCT in which 227 patients were randomly allocated to receive either ulinastatin (100,000 U) or a placebo immediately after ERCP (PEP incidence of 6.7% and 5.6%, respectively; p > 0.05) [17].

Reduction of pancreatic enzyme secretion

Somatostatin

The inhibition of exocrine pancreatic secretion can be obtained with somatostatin and its synthetic analog, octreotide. This hormone and its analog affect exocrine function directly by reducing the secretion of digestive enzymes, and indirectly by inhibiting secretin and cholecystokinin production. In addition to their antisecretory effects, somatostatin and octreotide have been demonstrated to modulate the cytokine cascade and may also have a cytoprotective effect on pancreatic cells, although the mechanisms of their cytoprotective effect remains unknown [18]. In an initial meta-analysis, somatostatin was found to be effective (OR, 0.38; 95% CI, 0.22 to 0.65) [12]. However, in a subsequent large-scale, multicenter, placebo-controlled trial with 382 patients, Andriulli et al. [13] found that a single dose of somatostatin at 750 μg, started 30 minutes before the procedure and continued for 2 hours afterwards, was ineffective in preventing pancreatitis; pancreatitis occurred in 11.5% of patients who received somatostatin versus 6.5% of those given a placebo. A meta-analysis of somatostatin, in which data from short- and long-term infusion studies were pooled, found somatostatin to be ineffective (OR, 0.68; 95% CI, 0.44 to 1.04; p = 0.075) [13,19]. A recent study from Spain showed that a bolus dose of 250 μg of somatostatin administered immediately before introducing the catheter into the papilla of Vater, did not help prevent post-ERCP acute pancreatitis [20]. Overall, the use of somatostatin did not reduce PEP.

Octreotide

Octreotide, a synthetic analog of somatostatin, has a much longer half-life [21]. It decreases the secretion of pancreatic enzymes and reduces intraductal pressure, and, possibly, proteolysis. However, octreotide increases the basal pressure and frequency of phasic contrac-

tions of the sphincter of Oddi and might contribute to pancreatic outflow obstruction and, hence, pancreatitis [22]. Serum levels peak at 4 minutes after intravenous infusion and within 30 minutes after a subcutaneous dose [21]. Of the published studies of octreotide, most have shown no significant reduction in the frequency of PEP compared with a placebo [21,23,24].

Relaxation of a sphincter of Oddi spasm

NG
NG is a nitric oxide donor with potent relaxant effects on smooth muscle, including the sphincter of Oddi [25]. The use of a low-cost drug such as NG to reduce the incidence of PEP is interesting in view of the potentially fatal cases that could be prevented. The influence of NG on the incidence of PEP was evaluated in two meta-analyses that pooled data from five RCTs involving 1,662 patients [26,27]. The studies were homogeneous, and both meta-analyses showed an overall significant reduction in PEP. In most patients, NG was administered transdermally. When the subanalysis was restricted to these patients, transdermal NG failed to show a significant reduction in PEP [9]. The use of NG was associated with a significant risk of transient hypotension and headache.

PDE type 5 (PDE-5) inhibitor
PDE-5 inhibitor is a smooth muscle relaxant. Beyond its original indication for erectile dysfunction [28] and other vascular diseases, including pulmonary artery hypertension [29] and Raynaud's phenomenon [30], clinical investigations have been expanded to include hypercontractile esophageal motility disorders [31] and biliary SOD [32]. PDE-5 inhibitor reduces basal sphincter of Oddi pressure [32]. The administration of PDE-5 inhibitor before ERCP may decrease sphincter of Oddi tone, allow easier cannulation, and ultimately reduce the occurrence of PEP. An RCT that included 278 patients undergoing ERCP showed no significant decrease in the rate of pancreatitis in the treatment group compared with the placebo group (8.0% vs. 7.8%, $p = 0.94$) [33].

Calcium channel blocker
Nifedipine, a calcium channel antagonist, was ineffec-

tive in two RCTs [34,35].

Interruption of the inflammatory cascade

NSAIDs
NSAIDs have anti-inflammatory mechanisms of action beyond the inhibition of prostaglandin synthesis. NSAIDs have been shown to be potent inhibitors of phospholipase-A2 (PLA2) activity in the serum of patients with acute pancreatitis when tested *in vitro* [36]. PLA2 catalyzes the hydrolysis of cell membrane phospholipids, leading to the production of numerous inflammatory mediators, and is believed to play a critical role in the initial inflammatory cascade in acute pancreatitis by generating prostaglandins, leukotrienes, kinins, and platelet-activating factor, which, in turn, lead to tissue damage and autodigestion of the pancreas [37]. PLA2 inhibition leads to the suppression of several important classes of proinflammatory lipids; thus, the use of PLA2 inhibitors has been considered an attractive therapeutic strategy in the treatment of inflammation-related diseases and tissue injury. Diclofenac is second only to indomethacin in its PLA2 inhibitory activity [36]. In patients undergoing high-risk ERCP, Murray et al. [38] reported a statistically significant protective effect for 100 mg of diclofenac, administered rectally upon arrival in the recovery area. However, that study showed no benefit in patients with SOD. A study by Cheon et al. [39] demonstrated no difference in PEP incidence between those given oral diclofenac (50 mg before and after ERCP) and a placebo in 207 predominantly high-risk patients (72% of patients had suspected SOD or underwent pancreatic therapy). Recently, a prospective RCT evaluating the protective effect of rectally administered indomethacin on PEP yielded a statistically conclusive result [6]. Of the 602 patients enrolled, the majority (82%) were suspected of having SOD. Overall, PEP occurred in 27/295 (9.2%) patients in the indomethacin group versus 52/307 patients in the placebo group ($p = 0.005$). This RCT showed that prophylactic rectal indomethacin significantly reduced the incidence and severity of PEP in patients at elevated risk for this complication. Whether the route of delivery of prophylactic NSAIDs affects the clinical efficacy is still an area of uncertainty. Suppository medications have reduced rela-

tive bioavailability compared with oral formulations for most drugs [40], attributable to erratic absorption and loss through the anal sphincter. However, by the oral route, drugs may be destroyed by gastric acidity. Delayed-release diclofenac (enteric-coated), as used in this study, resists dissolution at the low pH of gastric fluids but is rapidly released in the higher pH environment of the duodenum. It is completely absorbed from the gastrointestinal tract after oral administration, but the bioavailability is only about 50% to 60% because of extensive first-pass metabolism, possibly as a result of intestinal cytochrome P450 (CYP2C9, 3A4, and 3A5) [41]. After the oral ingestion of diclofenac, peak plasma levels are reached in about 2 hours (range, 1 to 4) in fasting healthy volunteers; on the other hand, peak plasma levels with rectal administration are reached within 30 minutes [39]. These time differences are probably significant clinically.

In summary, the prophylactic rectal administration of NSAIDs (indomethacin and diclofenac) may result in a substantial reduction in the incidence of PEP, translating into major medical and economic benefits.

OTHER ANTI-INFLAMMATORY DRUGS

Recombinant IL-10 has been evaluated for prophylactic immunomodulation of the proinflammatory cascade [42-44]. An initial RCT that included 144 higher-risk patients undergoing ERCP found lower rates of pancreatitis in each of two treatment groups (3% at 4 µg/kg and 5% at 20 µg/kg) versus the control group (11%, $p < 0.05$) [42]. Two subsequent trials did not confirm this benefit [43,44].

Xanthine oxidase inhibitors, such as allopurinol, might prevent PEP by inhibiting the generation of oxygen-derived free radicals. However, an RCT found no difference in the frequency of PEP in patients given allopurinol (12.1%) compared with those given a placebo (7.9%) [45].

A role for corticosteroids of various forms (methylprednisolone, prednisone, and hydrocortisone) has been investigated. Several RCTs with large numbers of patients demonstrated no benefit, or trend towards a benefit, for various corticosteroid formulations [45-47].

Heparin has a direct inhibitory effect on pancre-

atic proteases in both plasma and pancreatic tissue and improves pancreatic microcirculation during experimental pancreatitis [48]. The potential of subcutaneous heparin as a prophylactic agent for PEP has been evaluated in two RCTs that included 564 patients [49,50]. One of these, a prospective RCT that included 438 patients, found that low-molecular weight heparin did not result in even a trend towards a protective effect against PEP (8.8% vs. 8.1%, $p = 0.87$) [50].

CONCLUSIONS

There are many drugs that theoretically could have a role in the prevention of PEP and which may have shown promise in animal studies or even a single, randomized clinical study. When clinical studies are repeated elsewhere, however, the results are frequently disappointing. The most promising agents, NSAIDs (indomethacin and diclofenac) can reduce the incidence of PEP. Effective PEP prophylaxis has only been demonstrated using diclofenac or indomethacin administered rectally. NSAIDs are inexpensive and simple to administer, and encouraging results have been obtained with these agents. Indeed, today, routine rectal administration of diclofenac or indomethacin immediately before or after ERCP is recommended for the prevention of PEP. However, additional studies of NSAIDs with larger numbers of subjects are necessary to confirm the prophylactic effect and to establish whether these medications act synergistically with other prophylactic interventions, including pancreatic stenting.

Conflict of interest
No potential conflict of interest relevant to this article is reported.

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