New Advances in Preventing ERCP Induced Pancreatitis

- Identify patients at average and high risk for ERCP-induced pancreatitis.
- Define the desired properties of a drug used to reduce ERCP-induced pancreatitis (safe, effective, inexpensive and easily delivered).
- Identify agents that have been shown to reduce the frequency of ERCP-induced pancreatitis (gabexate, somatostatin and secretin).

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Introduction: Endoscopic retrograde cholangiopancreatography (ERCP) is the most dangerous endoscopic procedure routinely performed by gastroenterologists, with morbidity and mortality of up to 20+% and 1%, respectively. Of the various complications of this useful diagnostic and therapeutic procedure, post-ERCP pancreatitis (PEP) is rightly the most feared. Although the majority of cases of PEP are mild, 10-15% are severe, resulting in pancreatic necrosis, with its attendant local and systemic complications and certainty of prolonged hospitalization. The "Holy Grail" of ERCP is a drug that will prevent or abort the evolution of PEP. The "ideal" drug would be one which is effective, inexpensive, safe (low side effect profile) and easily administered (i.e. bolus or short infusion). The low incidence of PEP in some unselected patient groups makes "blanket" PEP prophylaxis costly (depending on the cost of the drug). Over the years, many pharmacologic interventions have been tried: most have failed, including anticholinergics, antihistamines, corticosteroids and antibiotics. The drugs that have been evaluated in controlled clinical trials are gabexate (n=3), somatostatin (n=3), octreotide (n=5), nifedipine (n=1), hydrocortisone (n=2), methylprednisolone (n=1), prednisone (n=1) and interleukin-10 (n=1). Three agents – somatostatin, its octapeptide analog, octreotide, and gabexate mesylate (a potent protease inhibitor) showed initial promise. Octreotide reduces hyperamylasemia but has not been shown to alter the clinical course of PEP. A meta-analysis of 28 clinical trials showed that both prophylaxis with

somatostatin and gabexate were effective in reducing the frequency of PEP. In a cost analysis, it was calculated that 13 patients would need to be treated with gabexate to prevent one case of PEP; the number for somatostatin was 27. However, in two large, controlled trials in which pharmacologic prevention was provided to high-risk patients, gabexate, somatostatin and octreotide were each found to be ineffective in preventing PEP. Gabexate is not universally available; the early treatment recommendation was for an infusion of this drug for 30-90 minutes pre-ERCP to 12 hours after it, clearly a logistic headache in a mainly outpatient population. A recent equivalence study showed that 0.5g of gabexate infused for 6 hours was as effective as 1g for 12 hours. A recent multicenter, prospective, randomized controlled trial of interleukin-10 (IL-10) was recent abandoned by the sponsoring drug company after a "futility analysis" revealed that insufficient cases of PEP were occurring in the study population (i.e. the study was likely to be underpowered). Newly-analyzed data from a randomized, controlled trial of synthetic secretin as PEP prophylaxis suggest that it may be effective in certain patient groups.

Secretin:

Secretin, a 27 amino acid polypeptide released in response to acidification of the duodenal lumen, stimulates secretion of water and bicarbonate from pancreatic ductal cells. Historically, secretin for clinical use was derived from porcine duodenums. Recently, a new synthetic porcine secretin has been developed that has been shown to be equally effective as a pancreatic secretagogue. Secretrin has been used for many years by ERCP endoscopists to improve their chances of cannulating the minor duodenal papilla in Pancreas Divisum [Devereaux]. Assessment of the degree of pancreatic injury in chronic

pancreatitis has also been studied using secretin stimulation [Conwell]. A fortuitous observation from historical data that patients who received secretin during ERCP appeared to be protected from PEP led a group at Duke University Medical Center to undertake a prospective, randomized, double-blind, placebo-controlled trial of secretin versus placebo. The results will be presented at Digestive Disease Week , 2003. Study patients undergoing ERCP were randomized to receive either placebo (8cc of saline) or 16 micrograms of synthetic secretin (in 8ml) . Patients with acute pancreatitis and known pancreas divisum were excluded. The study drug or placebo was administered at the time of inserting the duodenoscope and prior to cannulation in all patients, except those undergoing manometry, in whom it was given immediately after completing the pressure measurements. Patients were assessed in the immediate post-procedure period and by telephone 2-4 days later to determine if they had developed PEP, as judged by pain and supporting data. 1101 patients were enrolled in the study: 979 patients were randomized to receive placebo (491) or secretin (488). 122 patients were excluded, due to being lost to follow-up or because of protocol violations. There were 551 males and 428 females. Both groups were well-matched, except for pancreatic duct stenting, which was more common in the placebo patients. PEP was significantly reduced in the secretin group (44/488 vs 69/491, p=0.016). Secretin also had a highly significant effect in reducing PEP in patients who underwent biliary sphincterotomy (7/140 vs 33/159, P<0.0001) or cannulation of the common bile duct (27/361 vs 56/368). These are exciting and provocative data. They suggest that synthetic secretin, administered at the time of the procedure, may have a role in reducing the risk of pancreatitis is certain groups of patients, such as those in whom biliary sphincterotomy is indicated. Further studies,

looking a variety of dosing regimes and timing of secretin administration, are eagerly awaited.

Recommended Reading

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