EDITORIAL

A More Focused Approach to Pharmacoprevention of Post–Endoscopic Retrograde Cholangiopancreatography Pancreatitis

Efforts and courage are not enough without purpose and direction.

John F. Kennedy

In this issue of Clinical Gastroenterology and Hepatology, Kubiliun et al1 on behalf of the United States Cooperative for Outcomes Research in Endoscopy provide a systematic review and blueprint to guide clinical practice and inform future research for the pharmacoprevention of post–endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP). This article is timely, informative, and critically important because increasingly, emphasis on comparative effectiveness, cost containment, and high-quality health care delivery forms the standard for medical care in the United States.

Although not unique to the practice of gastrointestinal endoscopy, endoscopists have generally done a poor job in providing Grade A evidence for much of their past clinical practice. Relative to our colleagues in interventional cardiology for example, interventional gastrointestinal endoscopists have performed few robust trials evaluating important clinical outcomes. This is unfortunate because sometimes when our long-held beliefs about what constitutes best practice and optimal patient care are critically evaluated, the results are often surprising and practice changing.

For example, the EPISOD trial published in 2014 was a multicenter sham-controlled trial of 214 patients who had pain after cholecystectomy (so-called sphincter of Oddi [SOD] type III) and underwent either sphincterotomy or sham therapy.2 The authors found that sphincterotomy did not reduce disability caused by pain compared with sham and recommended against the use of ERCP and sphincterotomy for these patients. For 3 decades, interventional endoscopists had been touting the benefits of sphincterotomy for type III SOD, with considerable morbidity and occasional mortality attributed to this procedure. With the publication of the EPISOD trial, sphincterotomy for type III SOD has been debunked, and (hopefully) the practice has been abandoned. One can see other examples in the literature such as ERCP for drainage of the pancreatic duct in chronic pancreatitis, in which the results of well-designed trials were practice changing.3,4

The clinical problem of PEP is ubiquitous and one that nearly all interventional gastroenterologists face. Those of us who perform ERCP can almost assuredly remember those handful of patients who have suffered severe pancreatitis after this procedure. It is an often agonizing process of waiting for recovery through supportive care and management of complications. Fortunately, most patients with severe PEP recover.

The new focus on pharmacoprevention, which is highlighted by the well-designed trial of rectal indomethacin published by Elmunzer et al5 in 2012, should be warmly welcomed by everyone who performs ERCP. Although this study provided support for using rectal indomethacin in high-risk patients (pancreatic sphincterotomy, patients with previous PEP, clinical suspicion of SOD, pre-cut sphincterotomy, ampullectomy, more than 8 cannulation attempts, pneumatic dilation of an intact biliary sphincter), it did not definitively lend support to the use of rectal indomethacin in all patients. However, on the basis of this trial and others, the European Society for Gastrointestinal Endoscopy recommends rectal diclofenac or indomethacin for all patients without contraindication undergoing ERCP.6 Of note, in the United States there are currently no major society guidelines advocating their routine use, even in high-risk patients.

Despite few robust data to support the use of rectal nonsteroidal anti-inflammatory drugs (NSAIDs) for prophylaxis in average-risk patients, they are increasingly being used to prevent PEP in the United States.7 I think this is a mistake. Kubiliun et al1 point out that powering a trial of average-risk patients would require a very large sample size and that rectal NSAIDs have a benign side effect profile. However, we must perform this trial before declaring the effectiveness of this agent in all patients for several reasons. To make practice recommendations without evidence to support its use would be irresponsible; we have learned the determinant of making assumptions in the past (see SOD type III above) in regard to endoscopic practice and patient outcomes. In addition, endoscopists could be exposed to medical legal consequences if an average-risk patient develops PEP, and rectal indomethacin was not used.

Despite using rectal NSAIDs for high-risk patients, some still develop PEP. Therefore, although rectal NSAIDs are an improvement over giving nothing, careful investigation of other agents needs to performed. The authors have provided a classification system that organizes agents into “Promising” agents for which additional research should be performed, “Additional Exploratory” agents for which further investigation is necessary before committing to a randomized controlled trial, and “Lowest Priority” agents for those that are unlikely to be effective.

Although one could debate the categorization of the agents, a limitation that the authors acknowledge, the exercise of providing a blueprint for study represents the
true value of this article. In addition to prophylactic pancreatic stent placement, adjuvant pharmacoprevention strategies combined with rectal NSAIDs in high-risk patients may reduce PEP risk further. However, before a specific agent is chosen on which to focus, a more robust literature search, including obtaining the articles that were not retrievable or translatable in this review (up to 305 possible relevant studies in this article), will need to be completed.1

The authors provide an ambitious outline of how future clinical trials should be conducted: multicenter with well-defined outcomes, substantiated with power calculations, not using NSAIDS as a placebo, etc. What the authors did not address is the next step in how to perform these trials. Issues such as academic vs community participation and funding sources need to be considered when designing future prospective trials.

One important consideration is who will take ownership moving forward in terms of prioritizing study design. My suggestion would be a National Institutes of Health consensus conference and associated funding announcement that does not rely on the motivation of individual investigators. The field has gained considerable momentum in the last 5 years, and the National Institutes of Health may be the best vehicle to capitalize and expand on those gains.5

In conclusion, this systematic review is vitally important because it lends support to the need for cooperative comparative effectiveness studies of outcomes in endoscopy that are lacking in the United States. However, it takes several steps to organize and prioritize the direction in which the science of pharmacoprevention for PEP needs to move. If we are to achieve success in delivering higher quality care while reducing PEP cost, it will be by following a blueprint such as that provided in this review.

References

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