Management of Sphincter of Oddi Dysfunction: Teaching an Old SOD New Tricks?

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Although controversy has surrounded the existence and function of the sphincter of Oddi (SO) since its initial description by Rugero Oddi in 1887, animal studies, and to a lesser extent human studies, have subsequently confirmed its existence and clarified the important anatomic and physiologic functions of the sphincter [1]. The SO, located at the distal extremity of the bile and pancreatic ducts, is comprised of tonically active smooth muscle that controls the flow of bile and pancreatic juice into the second portion of the duodenum. During feeding, cholecystokinin (CCK) as well as other hormones and neurally mediated reflexes stimulate gallbladder contraction and pancreatic secretion as well as relax the SO. This coordinated activity enables bile and pancreatic secretions to enter the duodenal lumen in order to facilitate digestion and absorption [2].

Superimposed upon a SO basal pressure of 5–10 mmHg are phasic contractions of 100–150 mmHg. Since SO basal pressure is higher than duodenal basal pressure and phasic contractions of the SO are almost coincident with duodenal phasic contractions, the SO also prevents reflux of duodenal contents into the biliary and pancreatic ducts [3].

Over the past several decades, yet more controversy has embroiled this muscle: do abnormalities in SO function result in a clinical disorder? In particular, the SO has been implicated as a potential cause of post-cholecystectomy syndrome, i.e., recurrent symptoms of biliary pain that occur in 10–15 % of patients after cholecystectomy. SO

dysfunction (SOD) has also been proposed as an etiology for idiopathic recurrent pancreatitis and biliary-like pain in patients with an intact gallbladder without cholelithiasis. The proposed mechanism is functional obstruction from increased sphincter pressure due to spasm, hypertrophy, or denervation [1].

In the 1970s, the advent of endoscopic retrograde cholangiopancreatography (ERCP) served as an impetus for the development of miniaturized manometry catheters that could be passed through the working channel of a side-viewing endoscope and inserted into the biliary or pancreatic tree. In the 1980s, observational studies in humans using low-compliance manometry systems with multi-lumen catheters described several abnormalities in patients with suspected SOD including elevated basal pressure, a paradoxical rise in basal pressure with CCK injection, increased frequency of contractions with opiates, and abnormal retrograde contractions [4]. In 1988, Hogan and Geenan proposed the Milwaukee criteria for SO dysfunction or dyskinesia [5]. A revised version of their classification system that relied upon the presence or absence of elevated transaminases and bile duct dilatation during pain episodes was widely adopted. Patients with type 1 SOD had biliary-type pain, transaminases greater than twice the upper limit of normal, and bile duct diameter >12 mm during painful episodes. Type 2 SOD was defined as biliary pain plus only one of the two other criteria required to diagnose type 1 SOD. Type 3 SOD comprised patients with unexplained biliary pain with normal liver enzymes and normal caliber bile duct [5].

Surgical or endoscopic disruption of the biliary SO was a logical next step to treat SOD. Indeed, a randomized double-blind sham-controlled trial did demonstrate that patients with suspected type 2 SOD and high basal manometric pressures had significant and lasting

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improvement in pain following sphincterotomy when compared to sham therapy [6]. Based on limited evidence, manometric criteria were extended to justify sphincterotomy for type 3 SOD. Over the next several decades, the hallways of pancreaticobiliary clinics at tertiary referral centers seemed inundated by patients with suspected type 3 SOD referred for manometry. Yet, observational studies documenting a low rate of sustained pain relief and high risk of severe post-ERCP pancreatitis raised concerns regarding the utility and safety of manometry and sphincterotomy in type 3 SOD [7]. The results of the EPISOD trial, published in 2014, appeared to be the final nail in the coffin for the use of sphincterotomy in type 3 SOD. The authors of this multicenter study randomized 214 patients with type 3 SOD to receive sphincterotomy or sham therapy. Neither biliary nor dual biliary and pancreatic sphincterotomy provided sustained pain relief compared to sham therapy. Furthermore, abnormal manometric findings failed to predict treatment success [8]. Post-ERCP pancreatitis occurred in 11 % of patients in the sphincterotomy group despite prophylactic pancreatic stenting [8].

In the aftermath of the EPISOD trial, physicians were left with no effective treatment for patients with otherwise unexplained biliary-type pain. In this issue of *Digestive Diseases and Sciences*, the lead investigator of the EPISOD trial presents an open-label case series using duloxetine, a serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor approved to treat depression and anxiety, in 15 patients with type 3 and 3 patients with type 2 SOD (elevated transaminases) [9]. The rationale for the use of this antidepressant is based on the involvement of 5-HT and NE in visceral pain pathways. Duloxetine was prescribed at a dose of 30 mg daily for the first week followed by 60 mg daily. Patients were followed at 1-month intervals for 3 months. The primary outcome was the Patient Global Impression of Change (PGIC) score at 12 weeks. Of the 10 patients who completed the 3-month endpoint visit, 90 % reported a PGIC score of “much improved” or “very much improved.” Among the 14 patients who completed at least one follow-up visit, 64 % reported a PGIC score of “improved” or “very much improved.” Several additional patient-reported pain and disability scores were reported, including the RAPID, HADS, and SF-36 scores. Of note, ~40 % of patients (7/18) withdrew from the study due to adverse events including fatigue, nausea, rash, labile mood, and elevated liver tests.

The authors are to be commended for prospectively assessing a pharmacologic therapy for type 3 SOD, a vexing disorder for patients and clinicians alike. The sample size, though not large, is sufficient to serve as a basis for the design of a hypothesis-generating pilot study. The efficacy is similar to those obtained for the use of antidepressants to treat irritable bowel syndrome [10].

5-HT and NE reuptake inhibitors may modestly improve overall symptoms, but do not seem to be the “holy grail” sought as the ultimate treatment for SOD. A central challenge in developing an effective therapy for type 3 SOD is the still inadequate understanding of biliary sphincter physiology in health and disease as well as the mechanisms by which pain is generated and perceived. Furthermore, whether or not persistent post-cholecystectomy biliary pain is related to dysfunction of the SO remains controversial. Similar to the pain of chronic pancreatitis, nociceptive sensitization and cross-sensitization are equally attractive (and perhaps related) alternative hypotheses for the generation of biliary pain [11]. Significant tissue inflammation can activate nociceptive neurons, and if pain persists, result in nociceptive sensitization. Furthermore, persistent sensitization in one organ can sensitize the nociceptive pathway of an adjacent organ, i.e., cross-sensitization [11]. A more nuanced understanding of pain pathways in patients with SOD is needed.

The initial step in the evaluation of patients with suspected SOD as a cause of post-cholecystectomy pain remains a careful history and physical examination as well as exclusion of alternative explanations such as retained bile duct stone, peptic ulcer disease, and postoperative complications such as bile duct leaks or strictures. Once organic etiologies are excluded, pharmacologic therapies such as tricyclic antidepressants and duloxetine may provide adjunctive benefit, but remain secondary to building and maintaining a therapeutic relationship with the patient. In particular, dealing with concerns and fears about serious illnesses and understanding the psychosocial dimensions of the disorder increase the probability that patients leave the office reassured and educated. Definitive therapy of this vexing and baffling medical condition awaits the identification of therapeutic targets key to the genesis of pain in this disorder.

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