Selective-serotonin reuptake inhibitors for the treatment of hypersensitive esophagus

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Abstract: In patients with proton-pump inhibitor (PPI) resistant reflux symptoms, ambulatory 24 h pH impedance monitoring can be used to assess whether a relationship exists between symptoms and reflux episodes. Using this technique it has been suggested that patients with typical reflux symptoms and a normal upper endoscopy should be subclassified as follows: normal endoscopy and abnormal distal acid esophageal exposure (patients with acid reflux); normal endoscopy, with normal distal acid esophageal exposure and a positive symptom association for either acid or nonacid reflux (patients with hypersensitive esophagus); and normal endoscopy, normal distal acid esophageal exposure and a negative symptom association for acid and nonacid reflux (patients with functional heartburn). Although for patients with a normal endoscopy and abnormal distal acid esophageal exposure more aggressive acid suppression can be recommended, managing patients with hypersensitive esophagus and functional heartburn remains a real challenge.

Therefore, investigators have evaluated the role of tricyclic antidepressants or selective-serotonin reuptake inhibitors (SSRIs) in influencing esophageal perception. Imipramine has been shown to decrease pain perception in healthy male volunteers and improve symptoms of patients with chest pain and normal coronary angiograms. Trazodone improved symptoms in patients with esophageal contraction abnormalities, while administration of SSRIs lowered chemical and mechanical sensitivity and benefited patients with diffuse esophageal spasm. Furthermore, in a recent study conducted by our group, citalopram administered once daily for 6 months was effective in a select group of patients with hypersensitive esophagus, suggesting that there is a role for SSRIs in the treatment of this disorder.

Keywords: gastroesophageal reflux disease, hypersensitive esophagus, selective-serotonin reuptake inhibitors

Introduction

Gastroesophageal reflux disease (GERD) which is evident from symptoms or mucosal damage caused by the reflux of gastric contents into the esophagus is one of the most common chronic gastrointestinal diseases in Western countries [Hungin *et al.* 2009; Lagergren *et al.* 1999; Kahrilas, 1996]. The role of acid is well established in the pathogenesis of GERD and medical treatment of this condition is primarily based on gastric acid suppression by agents such as proton-pump inhibitors (PPIs) [Malfertheiner *et al.* 2006]. Despite frequent PPI use, physicians are faced with increasing numbers of symptomatic patients who do not respond to these medications [Mainie *et al.* 2006].

In patients with ongoing typical reflux symptoms (i.e. heartburn and/or regurgitation) despite acid

suppression, in whom endoscopy is normal, further testing with esophageal impedance combined with pH monitoring will help determine whether acid or nonacid reflux is present [Vela, 2009]. At the same time, a relationship between symptoms and reflux events can be distinguished [Sifrim *et al.* 2004]. Although more aggressive acid suppression can be used to try and manage patients with acid reflux, managing the other patients remains a real challenge.

GERD and nonerosive reflux disease

It is well known that in patients with reflux symptoms there is a lack of association between symptom severity/frequency and the presence or absence of esophageal inflammation [Smout, 1997]. Furthermore, there is no association between symptom severity and the extent of

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esophageal mucosal injury. Studies have shown that heartburn and regurgitation are as common in patients with erosive esophagitis grade I or II as in those with erosive esophagitis grade III or IV [Fass and Tougas, 2002]. In recent years, several population-based studies have demonstrated that up to 70% of patients reporting heartburn have no evidence of mucosal injury on endoscopy [Lind *et al.* 1997]. These patients, with classic GERD symptoms (heartburn and acid regurgitation) in the presence of a normal esophageal mucosa have been classified as having nonerosive reflux disease (NERD), which is also called endoscopy-negative reflux disease [Dent *et al.* 1999].

Endoscopy-negative reflux disease

NERD is a heterogeneous disorder and incorporates subgroups of patients who differ significantly in terms of presentation, pathophysiology and management. Because of this heterogeneity, previous trials have tried to differentiate patients with NERD on the basis of acid exposure using 24 h pH studies. Using traditional pH testing, investigators have demonstrated that 30–50% of patients with NERD presenting with heartburn do not show evidence of pathological acid reflux [Fass *et al.* 2001]. According to the Rome II criteria, these patients are classified as having ‘functional heartburn’. Specifically, the Rome II Committee for Functional Esophageal Disorders defined functional heartburn as an episodic retrosternal burning in the absence of pathological gastroesophageal reflux, pathology-based motility disorders or structural explanations [The Rome II International Working Teams, 2000]. However, this definition is vague and clearly does not provide any clues as to the different underlying mechanisms that may lead to heartburn in these patients. Patients with as well as those without any relationship between symptoms and acid reflux events are incorporated under the term functional heartburn. When it comes to understanding symptoms in GERD and specifically in patients with functional heartburn, a traditional ‘intraluminal’ view is insufficient. Other factors including central and peripheral neural mechanisms should be taken into account in order to understand the basis of the symptoms experienced by these patients [Fass and Tougas, 2002].

Mechanisms of GERD symptoms and esophageal hypersensitivity

Despite significant advances in our knowledge of the mechanisms leading to GERD, our understanding of the factors responsible for the symptoms of GERD remains limited. As previously described, many patients and healthy volunteers demonstrate multiple acid reflux events on pH testing, but often report few – if any – heartburn episodes. It has been estimated that no more than 5% of all acid reflux events (pH < 4) produce symptoms in patients with or without esophageal mucosal injury [Mattox and Richter, 1990]. This intriguing observation raises the obvious question of what in a specific acid reflux event leads to its conscious perception.

Several studies have recently speculated that central and peripheral neural mechanisms modulate esophageal perception. Psychological comorbidity (anxiety, stress, depression) can modulate esophageal perception and cause patients to perceive low-intensity esophageal stimuli as being painful [Fass and Tougas, 2002].

But is acid the sole culprit? There are mounting data to suggest that acid is no longer considered a prerequisite for heartburn to occur. Nonacid esophageal stimuli may also lead to the development of heartburn, as shown by studies with combined multichannel intraluminal impedance (MII) and pH monitoring [Hong and Vaezi, 2009].

The esophagus receives dual sensory innervation, traditionally referred to as parasympathetic and sympathetic, but more properly based on the actual nerves, vagal and spinal [Gebhart, 2000]. Vagal afferents in the esophageal smooth muscle are sensitive to mechanical distension, while vagal afferents in the mucosa are sensitive to a variety of chemical or mechanical intraluminal stimuli [Grundy and Scratcherd, 1989]. In general, vagal afferents do not play a direct role in visceral pain transmission at the level of the gut. In contrast, spinal afferents, which have their cell bodies in the dorsal root ganglia, are primarily acting as nociceptors and are central to the perception of discomfort and pain [Goyal and Hirano, 1996].

What leads to the development of esophageal hypersensitivity remains an area of controversy. Heartburn symptoms may represent activation of a common pathway in response to different intraesophageal stimuli. Hypersensitivity to

physiological amounts of acid appears to be the underlying mechanism for heartburn in the hypersensitive esophagus subgroup. This hypersensitivity to acid may stem from peripheral sensitization of esophageal afferents, leading to heightened responses to luminal stimuli or altered modulation of afferent neural function at the level of the spinal dorsal root or the central nervous system [Hollerbach *et al.* 2000]. Serotonin is an important neurotransmitter in the brain and in the gastrointestinal tract, where it plays a key role in the regulation of both sensory and motor functions [Kim and Camilleri, 2000]. Selective-serotonin reuptake inhibitors (SSRIs) act centrally and peripherally to enhance the availability of physiologically released serotonin and could theoretically benefit patients with hypersensitive esophagus [Gershon and Tack, 2007; Broekaert *et al.* 2006; Tack *et al.* 2003].

Functional heartburn and hypersensitive esophagus

In patients with ongoing symptoms despite acid suppression and normal endoscopy, it is desirable to perform reflux monitoring [Vela, 2001]. Measuring acid reflux by conventional pH monitoring in patients with acid suppression is not adequate because of the very low pretest likelihood of a positive test in this setting [Charbel *et al.* 2005]. Combined MII and pH testing represents a better tool under these circumstances because it detects both acid and nonacid reflux. Two MII–pH parameters may be used: the number of reflux episodes and the symptom association analysis. Normal values for the number of reflux episodes obtained by MII–pH are available, but the clinical significance of an abnormal number of acid or nonacid reflux episodes is unclear and treatment that normalizes the number of these episodes will not necessarily result in improvement if they are asymptomatic [Shay *et al.* 2004]. Therefore, a more clinically relevant question is whether there is a relationship between acid or nonacid reflux and symptoms. In order to answer this, the symptom index (SI) can be used. The SI is defined as the number of symptoms associated with reflux divided by the total number of symptoms. A positive SI is declared if it is at least 50% (i.e. at least half of the symptoms are associated with reflux) [Bredenoord *et al.* 2005].

A positive association between reflux (acid and nonacid) measured by MII–pH and symptoms is very important in differentiating patients with

ongoing typical reflux symptoms despite acid suppressive therapy. Utilizing data obtained with the use of MII–pH testing, it has been suggested that patients with typical reflux symptoms and a normal upper endoscopy should be subclassified as follows [Fass *et al.* 2001]: normal endoscopy and abnormal distal acid esophageal exposure (patients with acid reflux); normal endoscopy, with normal distal acid esophageal exposure and a positive symptom association for either acid or nonacid reflux (patients with hypersensitive esophagus); and normal endoscopy, normal distal acid esophageal exposure and a negative symptom association for acid and nonacid reflux (patients with functional heartburn).

According to population-based studies the proportion of patients with NERD as well as hypersensitive esophagus and functional heartburn appears to be 32% and 27% respectively [Savarino *et al.* 2009]. Although for patients with a normal endoscopy and abnormal distal acid esophageal exposure (patients with acid reflux) more aggressive acid suppression can be recommended, managing those with hypersensitive esophagus and functional heartburn remains a real challenge.

Selective-serotonin reuptake inhibitors in patients with hypersensitive esophagus

As expected, hypersensitive esophagus and functional heartburn usually do not respond to PPI therapy [Savarino *et al.* 2008], therefore it is essential that other treatment modalities are tried. In an effort to approach symptomatic esophageal dysmotilities and esophageal functional disorders from a different perspective, investigators have evaluated the role of tricyclic antidepressants or SSRIs to influence esophageal perception.

Peghini and colleagues [Peghini *et al.* 1998] were the first to report that imipramine decreases esophageal pain perception in healthy male volunteers. In this study, visceral perception for first sensation and pain was measured with intraesophageal balloon distension in 15 male volunteers. The effect of imipramine was studied in a double-blind, placebo-controlled crossover study. Imipramine was given in increasing doses (25 mg on days 1–3, 50 mg on days 4–6, 75 mg on days 7–12), with esophageal perception studied on day 13. According to the results, the balloon inflation volume at pain threshold was higher for the imipramine group ($p=0.015$).

Median intraballoon pressures at pain threshold were no different for the placebo and imipramine groups. Esophageal wall compliance was not affected by imipramine. The authors concluded that increased pain thresholds for the imipramine group in the absence of changes in esophageal tone imply the presence of a visceral analgesic effect.

Cannon and colleagues also showed that imipramine improved the symptoms of patients with chest pain and normal coronary angiograms, possibly through a visceral analgesic effect [Cannon *et al.* 1994]. A total of 60 consecutive patients underwent cardiac, esophageal, psychiatric and pain-sensitivity testing. These patients participated in a randomized, double-blind, placebo-controlled 3-week trial of clonidine at a dosage of 0.1 mg twice daily, imipramine at a dosage of 50 mg every night with placebo in the morning, or placebo twice daily. This treatment phase was compared with an identical period of twice daily placebo for all patients. During the treatment phase, the imipramine group had a mean reduction of 52% in episodes of chest pain, the clonidine group had a reduction of 39% and the placebo group a reduction of 1%, all compared with the placebo phase of the trial. Only the improvement with imipramine was statistically significant ($p = 0.03$).

Clouse and colleagues investigated the role of low-dose trazodone in patients with symptomatic esophageal contraction abnormalities [Clouse *et al.* 1998]. They demonstrated that patients receiving trazodone had a significantly greater global improvement of symptoms compared with those receiving placebo. A total of 29 patients with esophageal symptoms and contraction abnormalities of the esophageal body completed a 6-week, double-blind, placebo-controlled trial of trazodone (100–150 mg/day). Measures of esophageal and psychological symptoms were completed at entry and at each follow-up visit. Esophageal manometry was repeated at the end of the trial. Upon completion of the treatment, patients receiving trazodone ($n = 15$) reported a significantly greater global improvement than those receiving placebo ($n = 14$; $p = 0.02$). Manometric changes observed during the course of the trial were not influenced by treatment or by clinical response.

In a subsequent study, Handa and colleagues evaluated the role of SSRIs in patients with

diffuse esophageal spasm (DES) [Handa *et al.* 1999]. The cause of DES has not been clearly established, and effective treatment is lacking. To determine whether a psychosomatic approach can be effective in treating patients with DES, nine patients and 26 healthy volunteers were studied. Esophageal manometry and psychological testing were performed in both groups. The psychological background of the patients with DES was investigated. The authors started psychosomatic treatment with isosorbide dinitrate for 1 month, then prescribed SSRI antidepressants for an additional month. Anxiety and depression scores were substantially higher for the DES group than for the control group. Five of the nine patients with DES (56%) were diagnosed as having major psychiatric disorders. Only one patient showed improvement with isosorbide dinitrate, and eight patients improved with antidepressants. These initial observations suggest that psychosomatic treatment with antidepressants may be effective in the treatment of DES.

Finally Broekaert and colleagues evaluated the acute effect of citalopram on esophageal hypersensitivity, stating that administration of the drug lowered chemical and mechanical esophageal sensitivity, without altering the motility [Broekaert *et al.* 2006]. On two separate occasions, 10 healthy volunteers with established esophageal hypersensitivity underwent esophageal manometry with evaluation of mechanical and chemical sensitivity. They received placebo or citalopram 20 mg intravenously in a randomized, crossover, double-blind trial. According to the results, citalopram significantly increased the balloon inflation volume at pain threshold. It also significantly prolonged the acid perfusion time to induce perception of heartburn and discomfort.

Despite the encouraging evidence from the above trials, the role of SSRIs in the management of patients with hypersensitive esophagus has not been investigated so far. Therefore, in a recent study, we aimed to distinguish patients with hypersensitive esophagus by using ambulatory 24 h pH impedance monitoring and evaluate the effect of citalopram, a SSRI, on their symptoms [Viazis *et al.* 2011].

A total of 252 patients with normal endoscopy and typical reflux symptoms (heartburn, chest pain, regurgitation), despite PPI twice daily, underwent ambulatory 24 h pH impedance monitoring. Seventy-five patients with a normal distal

esophageal acid exposure time, but with a positive SI for either acid and/or nonacid reflux were classified as having hypersensitive esophagus and were randomized to receive citalopram 20 mg or placebo once daily for 6 months, while PPIs were discontinued. At the end of the follow-up period, 15 out of the 39 patients receiving citalopram (38.5%) and 24 out of the 36 patients receiving placebo (66.7%) continued to report reflux symptoms ($p=0.021$). It could be argued that the SI does not take into account the total number of reflux episodes and its cutoff of 50% is arbitrarily chosen, therefore the symptom association probability score should be more appropriate in these cases, while the extent of reflux and bolus clearance time were not measured. However, based on our results, we can conclude that treatment with SSRIs is effective in a select group of patients with hypersensitive esophagus.

Conclusions

In patients with NERD complete heartburn resolution after 4 weeks of standard dose PPI therapy ranges between 46% and 57% [Lind *et al.* 1997]. This surprisingly low response rate, which is 10–30% less than that reported in patients with erosive esophagitis, is mainly due to patients with hypersensitive esophagus and functional heartburn [Fass and Tougas, 2002]. In clinical practice most physicians will double the standard PPI dose; however, even this approach will not help the majority of patients. By using combined MII and pH monitoring we can now subclassify these patients. According to the results of recent studies, administering SSRIs seems to be a justifiable and beneficial option for those with hypersensitive esophagus. Whether this favorable effect of SSRIs could possibly extend to patients with functional heartburn remains to be seen in future studies.

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