Kosin Medical Journal 2015;30:1-11
http://dx.doi.org/10.7180/kmj.2015.30.1.1

KMJ
Review Article

Medical treatment of functional dyspepsia

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기능성 소화불량증의 치료

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Functional dyspepsia (FD) is a condition in which upper abdominal symptoms, such as epigastralgia, postprandial discomfort, and bloating, occur in the absence of any organic or metabolic disease that could explain the symptoms. The prevalence of FD is increasing, presumably because of an increasingly stressful environment, as well as overlap with other motility disorders such as gastroesophageal reflux diseases and irritable bowel syndrome. Numerous studies have attempted to determine the pathophysiological mechanisms of FD and establish effective FD treatment, with little success. Several therapeutic options have been explored, including *Helicobacter pylori* eradication, proton pump inhibitors, prokinetic agents, anti-depressant and anxiolytic agents, and acotiamide, a recent emerging drug. Through the many trials evaluating the efficacy of drugs for FD treatment, we found that it is necessary to treat according to the symptoms of FD and to use a combination of therapeutic options. Additional well-designed, prospective studies are needed to confirm the management of FD.

Key Words: Acotiamide, Disease management, Functional dyspepsia

Dyspepsia is one of the most prevalent gastrointestinal maladies, and patients with dyspeptic symptoms usually complain of heartburn, epigastralgia, postprandial discomfort, bloating, and a heavy feeling in the upper abdominal area. Some patients experience functional dyspepsia (FD) according to Rome III criteria, although results from upper endoscopy, abdomen ultrasonography, laboratory findings, computed tomography or other modalities do not show evidence of organic or metabolic diseases and are unable to shed light on the cause of these

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Received : Aug. 1, 2014
Revised : Oct. 3, 2014
Accepted : Oct. 8, 2014

Table 1. Rome III criteria for functional dyspepsia

Diagnostic criteria* for functional dyspepsia must include one or more of the following symptoms:
a. Bothersome postprandial fullness
b. Early satiation
c. Epigastric pain
d. Epigastric burning
And, there was no evidence of structural disease that is likely to explain symptoms (including at upper endoscopy).
1. Postprandial distress syndrome
Diagnostic criteria* must include one or both of the following symptoms:
a. Bothersome postprandial fullness, occurring after ordinary sized meals, at least several times per week
b. Early satiation that prevents finishing a regular meal, at least several times per week
- Other supportive criteria:
a. Upper abdominal bloating or postprandial nausea or excessive belching can be present
b. Epigastic pain syndrome may coexist
2. Epigastric pain syndrome
Diagnostic criteria* must include all of the following symptoms:
a. Pain or burning localized to the epigastrium of at least moderate severity at least once per week
b. The pain is intermittent
c. Not generalized or localized to other abdominal or chest regions
d. Not relieved by defecation or passage of flatus
e. Not fulfilling criteria for gallbladder and sphincter of Oddi disorders
- Other supportive criteria:
a. The pain may be of a burning quality but without a retrosternal component
b. The pain is commonly induced or relieved by ingestion of a meal but may occur while fasting
c. Postprandial distress syndrome may coexist

* Criteria must be fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.
This table is modified from reference 2, 15.

symptoms.[1,2] Rome III criteria divide FD into two diagnostic subcategories: epigastric pain syndrome (EPS) or postprandial distress syndrome (PDS). Symptoms of EPS are epigastric pain and burning, while PDS symptoms include early satiety, bloating, postprandial fullness and nausea (Table 1).[2,3]

Since 1998, when FD was first defined,[4] numerous studies have been conducted to determine the pathophysiological mechanisms of FD. Many experts in neurogastroenterology agree that FD is a multifactorial disease and can involve gastroduodenal motility, visceral hypersensitivity, psychosocial factors, high levels of gastric acid, the presence of *Helicobacter pylori (H. pylori)*, genetic factors, dietary factors and post-infectious conditions.[5] However, the pathophysiology of FD has not yet been es-

tablished.

Globally, the prevalence of uninvestigated dyspepsia and FD vary and have been reported in 7% to 45% and 11% to 29.2%, respectively.[6,7] In Korea, the prevalence of FD ranges from 8.1% to 22.3% in primary clinics, but FD prevalence in tertiary hospital-based studies was estimated as 24.8% and 40.5%.[7,8] In other words, the proportion of FD patients in tertiary hospitals was higher than FD patients at primary clinics, suggesting that many primary care physicians might still be uncertain about diagnosing or treating FD. Therefore, the goal of this paper is to review the medication of FD patients using current and emerging drugs for FD (Table 2).

Helicobacter pylori eradication

As mentioned above, *H. pylori* is considered a predisposing cause of FD. Several epidemiologic studies have reported that the *H. pylori* infection rate in FD patients was higher than in matched control populations. A meta-analysis expressed a 1.6 [95% confidence intervals (CI), 1.4 to 1.8] summary odds ratio (OR) for *H. pylori* infection in FD.[9] This suggests that eradication of *H. pylori* should improve FD symptoms, although this has not yet been confirmed.[10,11]

Despite the controversy surrounding *H. pylori* eradication therapy for FD patients, it is an accepted treatment worldwide. A Cochrane meta-analysis was performed on 17 randomized controlled trials and verified the association be-

Table 2. Drug classification used in functional dyspepsia

Classification
Histamine-type 2 receptor antagonists (H2RAs)
Proton pump inhibitors (PPIs)
Prokinetics
Dopamine receptor antagonists
Serotonin (5-HT) receptor agonists and antagonists
Motilin receptor agonists
Ghrelin receptor agonists
Muscarinic receptor antagonists
Antidepressants and anxiolytic agents
Tricyclic antidepressants (TCAs)
Selective serotonin reuptake inhibitors (SSRIs)
Selective serotonin and norepinephrine reuptake inhibitors (SNRIs)
5-HT1A agonists*

* 5-HT1A agonists also have prokinetic effects.

tween *H. pylori* eradication and improvement in FD symptoms (n = 3566). A small but significant benefit of *H. pylori* eradication therapy was observed, with a relative risk reduction of 10% (95% CI, 6% to 14%) and a number needed to treat of 14 (95% CI, 10 to 25).[12] In addition, recent systemic reviews and meta-analyses from China also demonstrated that the summary OR for improvement in FD patients after *H. pylori* eradication was 3.61 (95% CI, 2.62-4.98).[13] Unfortunately, there are no randomized controlled studies evaluating the effect of *H. pylori* eradication on FD in Korea, and the results of nonrandomized prospective studies that demonstrated the effect of *H. pylori* eradication are controversial.[7,14] A recent Korean study showed that *H. pylori* eradication (OR, 5.81; 95% CI, 1.07-31.59) and symptom improvement at three months (OR, 28.90; 95% CI, 5.29-157.82) were related to improvement of FD at one year.[15] The *H. pylori* infection rate is high in Korea, and in countries where the prevalence of *H. pylori* infection is >10%, the American Gastroenterological Association recommends *H. pylori* eradication as the initial management strategy for uncomplicated dyspepsia in patients younger than 55 years.[16] However, considering the side effects of antibiotic therapy, including antibiotic resistance, Korean clinical guidelines do not strongly recommend *H. pylori* eradication for FD and state that *H. pylori* eradication is best used in only a fraction of FD patients.[17,18]

Proton pump inhibitors

The reason for using proton pump inhibitors (PPIs) in FD is associated with gastric acid. A study from China reported pathological esophageal acid exposure in approximately 30% of FD patients and in 50% of those with epigastric burning.[19] In addition, pathological esophageal acid exposure has been reported in Belgian FD patients without heartburn symptoms.[20] Generally, suppression of gastric acid by PPIs improves epigastric pain and burning in patients with EPS symptoms.[21] Furthermore, even in patients with PDS symptoms, initial gastric acid emptying may function as the pathogenesis of symptom generation through the early onset of a duodenal break; therefore, acid suppression might result in a reduction of postprandial fullness.[22]

To the best of our knowledge, eight randomized controlled trials of PPIs versus placebo have been performed to date. A meta-analysis was performed using results from seven of these studies, which included 3725 patients (2387 PPIs patients, 1339 placebo patients), to evaluate the PPIs effect.[23] The study demonstrated that symptom relief achieved with PPI treatment (40.3%) was higher than that of a placebo (32.7%), and the number needed to

treat was 14.6 patients (95% CI, 8.7 to 57.1). In a subgroup analysis, PPIs were more effective than placebo in patients with 'ulcer-like' and 'reflux-like' symptoms, but there was no benefit of PPI treatment in patients with 'dysmotility-like' or unspecified dyspepsia. In randomized trials from Asia, a Hong Kong study failed to identify the efficacy of PPI over placebo in *H. pylori*-negative uninvestigated dyspeptic patients suffering from epigastric pain and discomfort.[24] A recent double-blinded, randomized, placebo-controlled study from Japan evaluated the effect of PPI on FD patients according to Rome III criteria and reported no significant difference between placebo and PPI groups in complete symptom relief for four major dyspeptic symptoms (epigastric pain, epigastric burning, early satiety, and postprandial fullness). However, symptom relief using PPIs was significantly superior to placebo according to a dyspepsia symptom questionnaire (45.3% and 28.2%, respectively, P = 0.027) and symptom diary assessment (48.7% and 30.0%, respectively, P = 0.016).[25] Therefore, the effect of PPIs on FD patients warrants further evaluation, especially in Asian populations.

Prokinetic agents

Prokinetic agents are a heterogeneous class of compounds that act via different types of receptors to increase gastric contractility.[3] Those include serotonin (5-HT) receptor agonists and antagonists, dopamine receptor antagonists, motilin receptor agonists, and ghrelin receptor agonists, to name a few. A Cochran review meta-analysis published in 2006 and including 19 randomized controlled trials of prokinetics reported a significant relative risk reduction of 33% (95% CI, 18% to 45%) compared with placebo.[26] However, previous studies on prokinetics in FD have several limitations including a high degree of heterogeneity, publication bias, and small sample size. In addition, most of the results were attained with cisapride, 5-HT4 receptor agonist, which has been restricted in the market due to adverse cardiovascular effects. Another 5-HT4 receptor agonist, mosapride was no better than placebo in a dose-finding study but is available in Korea and Japan.[27] Prucalopride, a potent 5-HT4 receptor agonist, is approved for treatment of chronic constipation. Unfortunately, it has not been thoroughly investigated in clinical FD trials, but prucalopride accelerates gastric emptying as well as small bowel and colonic transit in chronic constipation patients.[28]

In terms of the dopamine-2 receptor antagonists, a Phase III study of itopride reported similar findings; although itopride is available in Japan and Korea, it is no better than a placebo.[29] A recent meta-analysis from China that included nine randomized controlled trials

with a total of 2620 cases [1372 itopride treatment cases and 1248 placebo or other drug cases (control groups)] revealed that itopride had superior relative risk values of 1.11 (95% CI, 1.03 to 1.19; P = 0.006), 1.21 (95% CI, 1.03 to 1.44; P = 0.02), and 1.24 (95% CI, 1.01 to 1.53; P = 0.04) for global assessment, postprandial fullness, and early satiety, respectively.[30] However, the study had some of the limitations mentioned above, such as a large degree of heterogeneity.

A representative motilin receptor agonist, erythromycin might have therapeutic value in severe diabetic gastroparesis patients by shortening gastric-emptying times.[31] A randomized, double-blind trial was performed in both diabetic and idiopathic gastroparesis patients using mitemcinal, an orally active motilin agonist. Meal retention at 240 min showed a significant enhancement with 30 mg bid group (75%) compared with placebo group (10%), but gastroparetic symptoms improvement was not statistically different between mitemcinal and placebo groups.[32]

Ghrelin also has stimulating effects on gastric interdigestive motility and gastric emptying rate.[3,33] Both TZP-101, an injectable ghrelin agonist, and TZP-102, an orally administered ghrelin agonist, significantly improved gastric emptying rate and reduced postprandial symptom scores in diabetic gastroparesis patients.[34-36] However, a recent phase 2b, randomized, double-blind 12-week TZP-102 studies were not proved the efficacy of TZP-102 in diabetic gastroparesis compared with placebo.[37] The limitations of these studies have evaluated only in the patients with diabetic gastroparesis. Therefore, more researches are needed in FD patients using ghrelin receptor agonists. On the whole, prokinetic agents have the potential to enhance gastric emptying, but their efficacy in FD patients should be further explored.

Anti-depressant and anxiolytic agents

Tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), selective serotonin and norepinephrine reuptake inhibitors (SNRIs), and 5-HT1A agonists are effective in treating chronic pain syndromes[38] and irritable bowel syndrome (IBS),[39] but there is limited evidence of their effectiveness in treating FD. A crossover randomized placebo-controlled study of TCAs in seven FD patients with sleep disturbance identified that low-dose amitriptyline decreased gastrointestinal symptoms compared with a placebo.[40] However, the study had a small sample size, and the crossover design minimized the reported positive outcome.[16] A Chinese study only published in abstract evaluated low-dose imipramine for treatment of re-

fractory FD.[41] This randomized, double-blind, placebo-controlled trial is mentioned here because of the strength of the sample size. A total of 107 refractory FD patients (TCAs, n = 55; placebo, n = 52) were treated for 12 weeks. The symptom improvement rate after therapy was significantly higher in the imipramine group than in the placebo group (63.6% versus 44.2%, P = 0.02).

In terms of SSRIs and SNRIs, only one published trial has investigated the association between FD and SSRIs or SNRIs. A study from Netherlands assessed the efficacy of the SNRI venlafaxine in FD patients.[42] This study was a randomized, double-blind, placebo-controlled trial enrolling a total of 160 patients. The patients received either venlafaxine or placebo for eight weeks, and number and severity of symptoms, anxiety and depression, and health-related quality of life (HRQOL) were assessed before the start of treatment and at 4, 8, 12, and 20 weeks after treatment began. Dyspeptic symptoms, anxiety and depression, and HRQOL had improved after 20 weeks of medication therapy in comparison with baseline. Unfortunately, there was no significant difference between the venlafaxine and placebo groups, and the result was in agreement with those of previous study in Belgium.[43]

Several trials have reported that buspirone, a partial 5-HT1A agonist with anti-depressant and anxiolytic effects, enhances dyspeptic symptoms in FD.[5,44] A randomized, double-blind, placebo-controlled study was performed to examine the efficacy of tandospirone, a partial 5-HT1A agonist with anxiolytic activity, in improving the symptoms of Japanese FD patients.[45] In 144 patients with FD (tandospirone, n = 73; placebo, n = 71), improvement in abdominal symptoms scores (epigastric pain; epigastric discomfort; upper abdominal distention; bloating; early satiety; nausea and vomiting; appetite loss; and belching) were significantly larger in the tandospirone group than placebo group at weeks 1, 2, and 4.

Anti-depressant and anxiolytic agents are assumed to be effective in some proportion of patients with FD, but the actual efficacy has not yet been determined. However, a large, multi-center, randomized, placebo-controlled study (Functional Dyspepsia Treatment Trial; FDTT) is being carried out to determine whether 12 weeks of treatment with SSRI (escitalopram) or TCA (amitriptyline) improves FD symptoms compared to treatment with placebo, and initial results should be available this year.[46]

Acotiamide

Acotiamide, a muscarinic antagonist and cholinesterase inhibitor, is a new prokinetic agent that improves gastric motility and gastric emptying in the postprandial period.[16,47] Acotiamide

appears to act directly on the gut and indirectly through the brain-gut axis via actions in the central nervous system contemporaneous.[48] A multi-center, randomized, placebo-controlled, phase III trial of 892 FD patients with PDS was carried out in which acotiamide (100 mg) or placebo was administered three times a day for four weeks, with four weeks of follow-up after treatment. The purpose of this trial was to perform a global assessment of overall treatment efficacy (OTE) and elimination rate of all three meal-related symptoms (postprandial fullness; upper abdominal bloating; and early satiation).[49] The global assessment of OTE revealed a response rate of 52.2% in the acotiamide group and 34.8% in the placebo group ($P < 0.001$). Over the course of four weeks, the elimination rate for all three meal-related symptoms was higher in the acotiamide group than in the placebo group (15.3% versus 9.0%, $P = 0.004$). Another study was performed using real-time ultrasonography to determine the mechanism underlying the efficacy of acotiamide on gastric accommodation reflux (GAR) and gastroduodenal motility in patients with FD.[47] Of the 37 FD patients, 19 received acotiamide and 18 received a placebo. There was a significant difference in GAR between the acotiamide and placebo groups (21.7% versus 4.4%) after 400 mL ingestion of a liquid meal. Gastric emptying rate also increased significantly after subjects were treated with acotiamide ($P = 0.012$). These results suggest that acotiamide might be useful in FD patients, especially those with PDS. Large multi-national studies are needed to verify the mechanism of action.[1,16]

Conclusion

Drug therapies of FD are still difficult for many physicians and patients. *H. pylori* eradication might improve dyspeptic symptoms in some patients with FD in Korea, which is a country with a high prevalence of *H. pylori* infection. PPI treatment may result in improved symptoms in some FD patients, particularly those with EPS. Anti-depressant and anxiolytic agents are generally assumed to benefit patients with FD, but evidence supporting the efficacy of these drugs was not as strong as expected. Therefore, well-designed, prospective trials should be performed to determine the efficacy of anti-depressant and anxiolytic agents. Lastly, prokinetic agents are typically thought to benefit patients with the PDS subtype of FD, but this study was not able to confirm that established prokinetic agents alleviate FD symptoms. New prokinetic agents such as acotiamide may be useful in treating patients with FD. Management of FD must include treatment of the dyspeptic symptoms associated with FD, for which physicians should prescribe a combination of therapeutic treatments. Additional well-

designed, prospective studies and multi-drug (cocktail) therapies are needed to establish FD management practices.

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Peer Reviewers' Commentary

The prevalence of functional dyspepsia (FD) is increasing, presumably because of an increasingly stressful environment, as well as overlap with other motility disorders such as gastroesophageal reflux diseases and irritable bowel syndrome. Through the many trials evaluating the efficacy of drugs for FD treatment, it has been able to more easily adapt them for FD symptoms.

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