GI café

November 2012 Volume : 5 Issue : 2

SQUARE PHARMACEUTICALS LTD. BANGLADESH

Rabeprazole : New Era to treat Acid Related Disorders

Introduction

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Onset and power of acid inhibition

The five available PPIs differ in terms of acid stability, depending on various substitutes on the two ring structures. Table 1 shows the pKa of omeprazole, lansoprazole, pantoprazole and rabeprazole, the formation rate of acid-activated compounds at pH 1.2, their pump enzyme inhibitory potency in vitro, their acid transport inhibitory potencies in isolated gastric vesicles, and their relative clinical potencies based on 24 h intragastric pH. Rabeprazole has the highest pKa value of these 4 PPIs, and the rapid formation of acid-activated rabeprazole is due to partly its higher pKa. In an in vitro acid transport study, rabeprazole achieved maximal inhibition within 8 min of drug exposure, lansoprazole and omeprazole after 20 min and pantoprazole did not reach a maximum within 30 min. Interestingly, the rate of formation of acid-activated inhibitor correlates with the in vitro potencies of PPIs to inhibit gastric pump enzyme activity and acid transport across the vesicle membrane, and also correlates with clinical potency as determined by a comprehensive assessment of dose-dependent effects on intragastric pH. Differences in pKa also affect accumulation of PPIs. For example, rabeprazole accumulates to 6-fold higher levels than omeprazole (the difference in pKa values is 0.8). The higher accumulation of rabeprazole contributes to faster onset of inhibition of acid secretion, especially in older cells which weakly secrete acid (pH 3). Lysosomes have weakly acidic internal milieu due to the presence of the V-type proton pump, which has a completely different molecular structure to the P-type gastric pump. Rat kidney lysosome proton pumps were inhibited by a very high concentration of omeprazole in vitro (IC50 = 75 μM), indicating that lysosomal proton pumps do not have any essential Cys residues that can be blocked by PPIs activated within lysosomes. In vivo administration of omeprazole to rats at a dosage 5 times the ED50 for gastric acid secretion did not affect the function of liver lysosomes. Higher accumulation of rabeprazole in lysosomes compared with other PPIs may appear to be a demerit, but the lysosomal pumps are not inhibited by the intra-lysosomal presence of rabeprazole or omeprazole. In a comparative trial of 18 *H. pylori* negative adults, rabeprazole 20 mg reached a median 24 h gastric pH of 3.4, as compared with 2.9 for lansoprazole 30 mg, 2.2 for pantoprazole 40 mg, 1.9 for omeprazole 20 mg, and 1.3 for placebo (Table 2). Rabeprazole maintained a pH 4 for 8 h versus the other PPIs, which ranged between 3.0 and 7.4 h, P , 0.04. Rabeprazole has a rapid onset of action and achieves a maximal or near maximal effect.

Table 1. pKa, chemical activation, *in vitro* inhibition of pump activities and clinical efficacy of PPIs.

	Rabeprazole	Omeprazole	Lansoprazole	Pantoprazole
pKa (pyridine)	4.9	4.1	4.0	4.0
The formation rate (t_{50}) of activated compound at pH 1.2 (min)	1.3	2.8	2.0	4.6
IC_{50} in vitro inhibition of gastric proton	0.072	0.47		
Pump in isolated vesicles (mM)		0.2	0.4	0.6
The t_{50} of inhibition of acid transport in isolated vesicles (sec)	90	400	400	1100
Relative potencies compared to omeprazole based on 24-h intragastric pH (Caucasian population)	1.82	1.00	0.90	0.23

Clinical efficacy in the treatment of ARDs

Gastroesophageal Reflux Disease (GERD)

GERD is a common condition with an increasing prevalence in Western nations. In Japan, the prevalence of GERD has been on the increase since the end of the 1990s. The reasons for the increase in the reported prevalence of GERD may involve increased gastric acid secretion, a decrease in the *H. pylori* infection rate, increased awareness of GERD, and advances in the concept of GERD. Furthermore, although many GERD patients may present with typical symptoms such as heartburn and acid regurgitation, others may complain mainly of atypical symptoms such as epigastric pain or pressure, nausea/vomiting, hoarseness, chest pain, or wheeze. Symptom assessment, management and resolution remain the primary goals of medical intervention for both patients and physicians. Evaluation of the response of GERD symptoms to treatment, however, has been hampered by the lack of a valid, reliable, highly responsive, and easy to use assessment tool. We conducted a survey of the actual symptoms of Japanese GERD patients. A total of 124 patients with an endoscopic diagnosis of GERD completed a 50 part questionnaire (requiring only 'yes' or 'no' answers) that covered various symptoms related to the upper gastrointestinal tract, including psychosomatic symptoms. We extracted the 12 questions to which patients most often answered 'yes' and produced a multiple choice questionnaire that graded the frequency of each symptom (never = 0, occasionally = 1, sometimes = 2, often = 3, and always = 4), that we named the Frequency Scale for Symptoms of GERD (FSSG, Fig. 2). A significant reduction in the FSSG score occurs in patients with both mild and severe GERD after PPI therapy. The FSSG contains the 12 symptoms most commonly experienced by GERD patients, with 7 of the 12 related to reflux symptoms and the remaining 5 to dyspeptic symptoms. Sixty-eight GERD patients receiving proton pump inhibitor therapy completed the questionnaire before and after treatment for 8 weeks. A significant positive correlation was seen between reflux symptoms and acid related dyspepsia before and after therapy (r = 0.569 and r = 0.569; both P's, 0.001), and acid-related dyspepsia in patients with both NERD and RE. We concluded that GERD patients suffer not only from reflux symptoms, but also from acid-related dyspepsia, and PPIs improve both types of symptoms. The clinical efficacy of rabeprazole in the management of GERD has been evaluated in terms of symptom relief, healing and maintenance therapy of reflux esophagitis (RE), and in the symptomatic relief of non-erosive reflux disease (NERD) or uninvestigated GERD.

F-scale **F.S.S.G.(Frequency Scale for the Symptoms of GERD)**

* **Do you have any of following symptoms?**
If so, please circle the appropriate response below.

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	Question	Fill-in space				
		NEVER	OCCA-SIONALLY	SOME-TIMES	OFTEN	ALWAYS
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4	Do you sometimes subconsciously rub your chest with your hand?	0	1	2	3	4
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7	Do you have an unusual (e.g. burning)sensation in your throat?	0	1	2	3	4
8	Do you feel full while eating meals?	0	1	2	3	4
9	Do some things get stuck when you swallow?	0	1	2	3	4
10	Do you get bitter liquid (acid) coming up into your throat?	0	1	2	3	4
11	Do you burp a lot?	0	1	2	3	4
12	Do you get heartburn if you bend over?	0	1	2	3	4
	Please describe any other symptoms you experience.	SUM POINTS	+	+	=	

Acid reflux related symptom = POINTS

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Figure 2. The FSSG (Frequency Scale for the Symptoms of GERD) asks questions about the 12 symptoms most commonly experienced by GERD patients, with 7 of the 12 related to reflux symptoms and the remaining 5 to dyspeptic symptoms.

Reflux Esophagitis (RE)

Participants in studies evaluating rabeprazole for the acute treatment of erosive or ulcerative GERD were required to be symptomatic, with endoscopically confirmed lesions at (or prior to) study entry. Patients were administered rabeprazole 10 or 20 mg once daily or a comparator PPI or placebo for 1 or 4 weeks, with endoscopic assessment performed at baseline and after 4 and/or 8 weeks of study treatment in all but the week-long trial. Rabeprazole was effective in the acute symptomatic treatment and healing of erosive or ulcerative GERD

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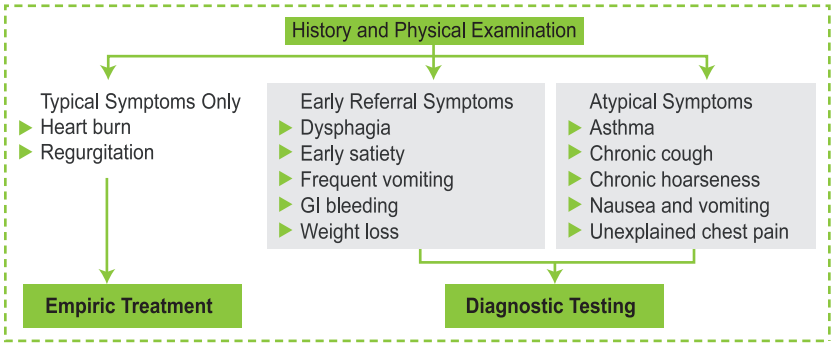
Acid-Related Disorders: Successful Management Strategies in Primary Care

INTRODUCTION

Acid-related disorders are both common and increasing in primary care practice. Left untreated, GERD can progress to erosive esophagitis, Barrett's esophagus, and esophageal adenocarcinoma. Medical management of GERD is compensatory, not curative. Current medications do not address the underlying esophageal motor dysfunction, but prevent the symptoms and complications of reflux. Patients with GERD require long-term maintenance with medication. Although the focus of GERD treatment has shifted from healing erosive esophagitis to controlling symptoms, PPIs are still the mainstay of therapy. Long-term data show that these agents generally are safe, although minor concerns exist with regard to their impact on osteoporosis and an association with Clostridium difficile colitis. When patients are refractory to PPI treatment, clinicians should consider causes other than reflux disease, such as hypersensitivity of the esophagus or functional heartburn.



Diagnostic Approaches

For patients with the typical GERD symptoms of heartburn and regurgitation, primary care providers may initiate a trial of PPI therapy. Referral for diagnostic testing is warranted when patients have alarm symptoms or other symptoms outside the typical picture of GERD. However, a trial of empiric therapy may be indicated for certain patients with atypical symptoms. For example, if a patient with chronic cough, hoarseness, or laryngitis is not responding to appropriate therapies and questioning elicits a GERD symptom profile, it would be reasonable for the primary care clinician to initiate PPI therapy and evaluate the response before referring the patient for endoscopy or pH monitoring.Diagnostic techniques for GERD include endoscopy, ambulatory pH monitoring, esophageal manometry, and barium esophagogram. Each of these tests has its place in investigating different aspects of reflux disease. Techniques most often used are endoscopy and esophageal pH monitoring.

Acid-Suppression Therapy

For most patients, acid-peptic disorders, including GI effects of NSAIDs, can be managed with medical therapy in the primary care setting. Currently, acid suppression, which is the primary goal of GERD treatment, relies on 2 classes of agents: histamine2-receptor antagonists (H2RAs) and PPIs. Antacids, which alter the pH of the refluxate but not through acid suppression, are of limited use beyond supplemental or rescue therapy in patients with anything worse than mild GERD symptoms.

A Long-Term Condition Needs Long-Term Treatment

Most patients with GERD need long-term treatment. After erosive esophagitis has been healed with acute PPI treatment, therapy must continue to maintain healing. A Cochrane literature review confirms that maintenance therapy with the same PPI dose used acutely to heal erosive esophagitis is most effective in preventing relapse.

When Patients Don't Respond to Acid-Suppression Therapy

There is no consensus on what constitutes lack of response to PPI treatment. Judgment differs according to the clinician's preference and the patient's satisfaction. However, several investigators consider lack of response to be persistent symptoms despite treatment with double the Food and Drug Administration (FDA)-approved standard dose of a PPI. An abnormal pH monitoring test (ie, an abnormal level of EAE) in patients taking double-dose PPI therapy is rare. Therefore, if pH testing is necessary, it should be delayed until after the conclusion of a trial of double-dose PPI. Conclusion Finally, there are patients for whom every test is normal and there is no symptom correlation to EAE. These patients are deemed as having functional heartburn and require a change in therapeutic approach. Psychological approaches, including low-dose antidepressants, biofeedback, and hypnotherapy, may help these patients.

Ref: http://www.practicingclinicians.com/CPCE38807_7E_GERD.v7.pdf

Stress and Peptic Ulcer Disease

ALEXANDER THE GREAT DIED AT THE age of 32 years, with acute abdominal pain that began after several days of binge drinking. Might it have been from a perforated peptic ulcer?

Founding a great empire may be an extraordinary example of life stress, but stress is currently out of fashion as a cause of ulcer. For many years the dominant etiologic model was exquisitely psychosomatic: a vulnerable person-on grounds of personality and pepsinogen-encounters a major life stress, and a duodenal ulcer is born. But after *Helicobacter pylori* proved to be a key and curable element in the ulcer diathesis, many concluded that the "real" cause had been found and had nothing to do with psychology. Research into stress effects on ulcer fell off precipitously, and the earlier literature was dismissed as misguided and naive, given the new, respectable status of peptic ulcer as an infectious disease. In a recent telephone survey of ordinary Americans' views of what causes an ulcer, the authors seemed to consider the widespread belief in a psychological component tantamount to a superstition deserving eradication. But attempts to explain ulcer using *H. pylori* and Nonsteroidal Antiinflammatory Drugs (NSAIDs) as sole etiologic factors are destined to fail. More than 80% of *H. pylori*-infected people (and the vast majority of NSAID users) never develop an ulcer, while at least 10% of patients with non-NSAID-related peptic ulcers have no *H. pylori* infection. The field is therefore open for other factors working in conjunction with *H. pylori* or causing ulcers through alternative pathways.

The evidence that psychological stress is of those factors is not invalidated by the discovery of *H. pylori*. The German blitz in London, the Kobe earthquake, economic crisis in Sophia, and sovereignty negotiations in Hong Kong have all been followed by an increase in peptic ulcers in both the stomach and the duodenum, as has being a prisoner of war. In defined epidemiologic cohorts, subjects with psychological distress, self-described "stress or strain," or concrete life stressors at baseline have increased incidence of ulcer over 9 to 15 years, an association that holds up to adjustment for a variety of nonpsychosocial risk factors and is similar whether the outcome is assessed by medical records or by self-report.

Among potential mediators, several known behavioral risk factors for ulcers-smoking, alcohol abuse, and lack of sleep-have clear associations with real-life stress and are known to impair wound healing through their effects on immune function; sleep loss can also elevate cortisol levels. Individuals under stress may also be likely to increase NSAID use. On the physiological side, stress is known to modify gastric blood flow, which plays an important role in the gastric mucosal barrier and to affect possible mediators such as thyrotropin releasing hormone, cytokines and corticotropin-releasing hormone.

In most ulcer cases where stress is involved, *H. pylori* is likely to be present as well. The impact of the 2 factors may be additive. Individuals infected with large burdens or particularly virulent strains of *H. pylori* may be capable of developing ulcers regardless of their psychological characteristics, whereas persons under severe stress might develop ulcers despite light or nonexistent infection. Psychological stress may also promote the growth of *H. pylori* in the duodenum if it increases duodenal acid load, since the *H. pylori*–inhibitory effects of bile seem to be reversed by acid. A tantalizing line of research has illustrated the adverse effects of stress on the course of various infections; in the case of *H. pylori*, where primary infection occurs chiefly during childhood, stress-triggered exacerbation of the pathology induced by the bacteria, via psychoneuroimmunologic or other mechanisms, could be a cofactor.

Research into the influence of stress on wound healing elsewhere in the body lends insight into possible mechanisms. Restraint-stressed mice heal more slowly than control mice, with lower leukocyte infiltration of their wound sites, apparently because of increased glucocorticoid secretion affecting proinflammatory cytokines; even physiologic variations in plasma cortisol can significantly alter cytokines important for wound healing and gastrin release.

In humans, healing of both epidermal and mucosal wounds is impaired by stress. Caregivers for relatives with Alzheimer disease took an average of 24% longer than well-matched controls to completely heal a small, standardized skin wound, and mucosal wounds placed in dental students 3 days before academic examinations healed 40% more slowly than those made during summer vacation. In both cases stress was associated with impaired production of interleukin 1 (IL-1) in response to lipopolysaccharide stimulation; IL-1 also plays an important role in *H. pylori*- induced inflammation and in gastrin secretion. Like most diseases, it has a multifactorial origin: the grammar of etiology is usually not either/or but and, although the proportions of various contributing factors will vary from 1 patient to another. Clarification of the role of stress in peptic ulcer must of course take *H. pylori* and NSAIDs into account. The research community is rising to the challenge, with a diversity of groups designing studies in animal models, clinical populations, normal subjects, and epidemiologic groupings to see whether, as the present panel concludes, reports of the death of ulcer psychosomatics have been greatly exaggerated.

Ref: http://pni.osumc.edu/KG%20Publications%20(pdf)/129.pdf

Congratulations!

The Winners of GI café Quiz Competition

(June 2012 Volume : 5 Issue : 1)

1. **Dr. Minhaz Uddin**
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   14/2 Gongadhor Potty, Manikganj

2. **Dr. Shakhawat Hossain**
   MBBS, BCS (Health)
   PGT (Medicine & Chest)
   FCPS (Medicine)
   Sadar Hospital, B. Baria

3. **Dr. Sanjida Afroj**
   Assistant Registrar (Gynae. Dept.)
   Central Medical College & Hospital
   Comilla

4. **Prof. Dr. Faridul Alam**
   MBBS, FCPS, DME (UK)
   Shahjalal Diagnostic Clinic
   143 SK Mujib Road
   Agrabad, Chittagong

5. **Dr. Md. Nuruzzaman Khokon**
   MS (Ortho.)
   Shakhipur, Tangail

Editorial Note:

Dear Doctor, It's our immense pleasure to inform you that we have published the first issue, 2012 of GI Café. In this issue we try to focus the various aspects like Rabeprazole : New Era to treat Acid Related Disorders, Acid Related Disorders : Successful Management Strategies in Primary Care & Stress and Peptic Ulcer Disease. Your comments and suggestions will enrich our upcoming issues. Please participate in quiz competition and win prizes.

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