Digestive Diseases and Sciences (2019) 64:4–6
https://doi.org/10.1007/s10620-018-5288-9

EDITORIAL

Optimal PPI Dosing for Improving GERD Symptoms: Is Timing Everything?

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Published online: 20 September 2018

Background and Significance

There have been a large number of clinical studies published regarding the effect of proton pump inhibitors (PPIs) on acid secretion; it is generally accepted that gastroesophageal reflux disease (GERD) symptoms are most often related to esophageal acid exposure [1, 2]. Furthermore, for once-daily PPI administration, morning administration is superior to evening administration [3, 4]. GERD patients also differ in relation to acid sensitivity [2]. Importantly, PPIs also vary greatly in relative potency [5], expressed as differences in the percentage of time the intragastric is ≥ 4 throughout a 24-h day (pH > 4-time) [5]. One key variable is also the timing of a PPI dose relative to a meal, under the hypothesis that peak PPI serum concentrations should coincide with maximal postprandial proton pump activation [6].

In this issue of *Digestive Diseases and Sciences*, Waghray et al. [7] investigated the effect of changing the time of administration of PPIs on GERD symptoms. They defined taking a PPI 20–30 min before breakfast as "optimal" timing; taking it at some other interval was termed "suboptimal." The main outcome variable was improvement in gastroesophageal reflux disease symptom assessment scores (GSAS). Subjects were recruited from patients taking PPIs suboptimally with persistent GERD symptoms. Subjects continued to take 20 mg of omeprazole daily using the suboptimal pattern of administration; after a 2-week run-in period, symptoms were scored. Then, 64 subjects were randomized to take 20 mg of omeprazole 20–30 min before breakfast (24 subjects) or to continue the suboptimal pattern of administration. After 4 weeks, the GSAS was repeated. The study ended for those receiving optimal therapy and the 40 subjects receiving suboptimal therapy were re-randomized to either continue suboptimal therapy (23 subjects) or take 20 mg of omeprazole 20–30 min before breakfast (17 subjects). After an additional 4 weeks, the GSAS was again calculated. Overall, they report that GSAS improved for those receiving PPI therapy 20–30 min before breakfast compared to those taking it at other times. Assuming that these results were generalizable to all PPI users, they then used the results in a cost model for PPI use in the USA, concluding that if all US patients took their PPIs 20–30 min before breakfast, it would produce a more satisfied patient population and could save more than 4 billion USD annually [7].

Controversies

The Waghray et al. study was based on the belief that the timing of PPI administration in relation to the morning meal is an important variable in terms of PPI effectiveness and that their results were generalizable to all patients taking a variety of PPIs for GERD. Their hypothesis should be evaluated in terms of preexisting data; for example, the effect of PPI administration in relation to breakfast on intragastric pH was previously studied by Brummer et al. [8] who found that the potential benefits were limited to the first few days of therapy. Boltin et al. [9] also addressed the effect of timing of PPI use on GERD symptoms when they gave 40 mg of esomeprazole to GERD patients 30 min before or after breakfast, reporting no difference in symptom control. These studies suggest that the optimal administration timing hypothesis is neither an essential nor generalizable determinant of symptomatic response in GERD patients and that universal institution of optimal timing of PPI administration is unlikely to provide a substantial cost saving. How then can we put the Waghray et al. observations into perspective?

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Waghray et al. focused on a particular subgroup of subjects (i.e., those with GERD-like symptoms who achieved an incomplete clinical response to PPI therapy not taken 20–30 min before breakfast [7]). Their population was incompletely described; for example, they specifically excluded those with normal upper endoscopy within 1 year, Barrett's esophagus, or strictures, but did not specify whether all had endoscopy nor what proportion had erosive esophagitis, or whether they included patients with functional reflux. Their premise was that their intervention improved the effectiveness of pH control, which in turn improved the observed outcomes. Nevertheless, the authors did not provide objective evidence of a consistent effect on any physiologic measure such as cumulative esophageal acid exposure. Although some subjects received instructions in order to standardize patient instructions and expectations (e.g., you have symptoms because you were not taking the drug properly), the authors did not state whether a unified script was used. The study included randomization regarding the timing of PPI administration, but the design did not fully prevent bias: for example, to distinguish between improvement resulting because the physician "changed something" versus improvement related to a change in timing of PPI administration would require a different design such that each subject could receive a pill before and after breakfast consisting of the PPI and an identical placebo in order to prevent subjects being aware of when the PPI was given.

The Waghray et al. study specified a relatively low PPI dose (20 mg of presumably generic omeprazole). In contrast, the Boltin et al. study specified a high dose of 40 mg of esomeprazole which is equivalent to 64 mg of omeprazole with median intragastric pH > 4-times of ~ 45% and 60%, for these doses of omeprazole and esomeprazole, respectively) [5, 9].

It is unclear whether GERD patients with inadequate symptomatic response to low-dose PPI therapy fit a characteristic profile in terms of acid secretion, esophageal acid sensitivity, or esophageal acid exposure. While the group means of intragastric pH in response to PPI therapy are reproducible [10], there is considerable individual variation such that the mean or median pH > 4-times are only of limited usefulness when discussing an individual patient [11]. As shown in Fig. 1, the grouping of subjects with high or low pH > 4-times remained recognizable when tested (in this example) with a different PPI. This question can probably be answered from the data available within the large number of published studies addressing this issue.

Heterogeneity among GERD patients may also affect outcomes. For example, the Boltin et al. study [9] evaluated apparently average GERD patients, whereas Waghray et al. [7] studied patients with persistent heartburn while taking a PPI and with a defined pattern of timing of PPI ingestion termed suboptimal. There are numerous potential causes of an inadequate response to PPIs; to obtain generalizable results will likely require inclusion of patients characterized by parameters such as acid secretion measurements, pH > 4-times, esophageal acid exposure measurements, mucosal impedance, the presence or size of a hiatal hernia, enhanced esophageal acid sensitivity, or other reproducible anatomical characteristics and physiological measurements. For those with a high rate of gastric acid secretion, lengthy or very highly acidic esophageal pH exposures, and/or low pH > 4-times PPI effectiveness would likely be a critical variable, and we believe it is likely that improvement would relate to increase the omeprazole equivalents administered

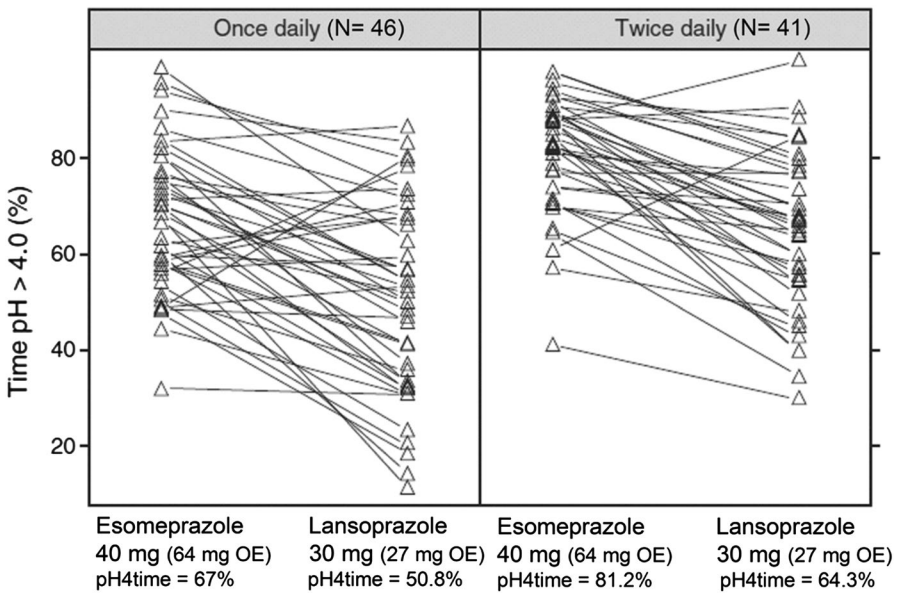

Fig. 1 Percentage of time during the 24-h monitoring period the intragastric pH < 4 stratified by treatment regimen. The omeprazole equivalents, OE, are shown for each PPI [5] as well as the mean pH 4-time. Adapted from Spechler et al. [11]

once or twice daily. This approach has been shown to increase pH > 4-time [5] and symptom response [12]. Further studies of large group of patients with what is considered to be inadequate PPI responses are needed to allow reliably identify subgroups for which specific therapy can be tailored to their primary abnormality, which in turn would enable the construction of reliable treatment algorithms.

Recommendations

One unproven assumption regarding persisting GERD symptoms while receiving PPI therapy is that the majority of sufferers have symptoms due to continuing esophageal acid exposure. Traditionally, the initial approach has consisted of physical maneuvers to reduce acid reflux such as elevation of the head of the bed, the elimination of late evening meals and smoking, a change in the timing of PPI administration, or in the recommended dose and type of PPI. Understanding relative PPI potency in terms of improving pH > 4-time increases PPI effectiveness by increasing the omeprazole equivalents administered, the frequency of PPI administration, or both. Omeprazole equivalents can be increased by increasing a PPI's dose or substitution of a more potent PPI [5]. The most marked increase in pH > 4-time is obtained by using twice-a-day dosing (i.e., approximately 10 mg of omeprazole twice a day is equivalent to 40 mg of esomeprazole or rabeprazole once a day.) [5]. Since PPIs also vary remarkably in cost to the patient, it should be possible to select a combination of PPI and once or twice-a-day dosing that is most cost-effective in any specific locality.

Summary

The Waghray et al. [7] study was a small study seeking a simple answer to a large and very complex question. The conclusion that in chronic usage, the importance of the timing of PPI administration in relation to breakfast (i.e., optimal administration) is the primary determinant of outcome appears either false or, at least, not generalizable. The notion that standardization of the timing of PPI administration will improve overall patient satisfaction and markedly reduce costs also seems unlikely. Nonetheless, this study brings attention to the important problem of failure to achieve symptom relief for some GERD patients and undoubtedly will stimulate many additional studies.

Funding Dr. Graham is supported in part by the Office of Research and Development Medical Research Service Department of Veterans Affairs, Public Health Service Grant DK56338 which funds the Texas Medical Center Digestive Diseases Center.

Compliance with ethical standards

Conflict of interest Dr. Graham is a consultant for RedHill Biopharma regarding novel *H. pylori* therapies. He has also received research support for culture of *Helicobacter pylori* and is the PI of an international study of the use of antimycobacterial therapy for Crohn's disease. He is also a consultant for BioGaia in relation to probiotic therapy for *H. pylori* infection and for Takeda in relation to *H. pylori* therapies.

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