CONTROL OF ESOPHAGEAL AND INTRAGASTRIC PH WITH COMPOUNDED AND MANUFACTURED OMEPRAZOLE IN PATIENTS WITH REFLUX ESOPHAGITIS: A PILOT STUDY

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ABSTRACT

Background
Proton pump inhibitors (PPI) are the drugs of choice for treatment of gastroesophageal reflux disease (GERD). Omeprazole, the first PPI commercialized, is now available in different formulations.

Objectives
To compare the efficacy of different omeprazole formulations on gastric acid secretion measured by intragastric and esophageal pH monitoring in patients with reflux esophagitis.

Methods
Prospective, open, randomized clinical trial involving *H. pylori* negative patients with typical symptoms of GERD. Patients were submitted to 24-h intragastric and esophageal pH studies during use of six different formulations of compounded and manufactured omeprazole.

Results
Thirty patients, 19 female, median age 55 years were studied. The intragastric pH was maintained below 4.0 for a median of 36.7% of total time in compounded group and 47.7% in manufactured group ($p>0.05$). There was also no statistical difference between the median percentage of time of pH below 4.0 in orthostatic and supine position in compounded and manufactured groups (30.1% and 49.6% and 28.8% and 55.2%, respectively). The esophageal pH was maintained below 4.0 for a median of 0.1% of total time in compounded group and 0.4% in manufactured group ($p>0.05$). In orthostatic position the median percentage of time of esophageal pH below 4.0 was 0.0% in both groups ($p>0.05$). In supine position, the median percentage of time of esophageal pH below 4.0 was 0.1% and 0.3% in compounded and manufactured groups, respectively ($p>0.05$).

Conclusion
The omeprazole formulations studied (compounded and manufactured) showed similar control of gastric acid secretion and esophageal acid exposure in patients with reflux esophagitis.

Key Words: *Omeprazole/therapeutic use; gastroesophageal reflux/drug therapy; esophageal pH monitoring; gastric acidity determination*

Proton-pump inhibitors (PPIs), substituted benzimidazoles, are irreversible blockers of the activated H+/K+ ATPase (or proton pump) that potently suppress gastric acid secretion. Since their introduction, PPIs have become the drug of choice for the treatment of acid-peptic disorders, especially gastroesophageal reflux disease (GERD). Today, it is known that PPIs promote the

healing of esophageal erosions secondary to GERD in 80% to 90% of cases, in addition to symptom relief in most of these patients.[1-3]

In a meta-analysis, Bell et al.[4] demonstrated that the efficacy of PPI in the treatment of GERD is intimately related to the capacity of the drug to inhibit gastric acid secretion measured by prolonged intragastric pH monitoring. In this respect, the total time of intragastric pH higher than 3 or 4 represents an excellent predictor of symptom improvement and healing of esophageal lesions in patients with reflux esophagitis.[5] In addition, the nocturnal decline in intragastric pH observed during the use of PPI associated with GERD may explain the therapeutic failure in some patients.[6]

Omeprazole was the first PPI available and has been commercialized by AstraZeneca since 1988. The world patent for this drug expired at the beginning of 2001; but several non-original and compounded formulations of this PPI were available on the market even before this date. In Brazil, the manipulation of capsules containing omeprazole salts imported mainly from China and India by compounding pharmacies is very common. These compounded drugs are widely commercialized in Brazil, especially among patients with GERD, who require chronic use of antisecretory drugs. This fact is mainly the result of the low cost of these medications when compared to manufactured drugs. As a rule in Brazil, manufactured omeprazole is, on average, 2 to 8 times more expensive than the compounded drug.

The objective of this pilot study was to compare the efficacy of the control of intragastric and esophageal pH in patients with reflux esophagitis using different omeprazole formulations commercialized in Brazil.

MATERIAL AND METHODS

This open, randomized clinical trial was conducted at Instituto Alfa de Gastroenterologia, Hospital das Clínicas, Universidade Federal de Minas Gerais (UFMG), after approval by the Ethics Committee of UFMG (protocol ETIC 385/07) from June to December 2007. Patients included in the study received detailed information about its objectives and signed a free informed consent form.

Inclusion and Exclusion Criteria

The patients were selected according to the following inclusion and exclusion criteria: criteria for inclusion in the study were age older than 18 years; typical symptoms of GERD characterized by the presence of heartburn and acid regurgitation at least twice a week, which responded satisfactorily to previous omeprazole administration; absence of *Helicobacter pylori* infection documented by the ^{13}C urea breath test (UBT) performed after discontinuation of antisecretory drugs for at least 10 days; upper gastrointestinal endoscopy showing no endoscopic or hystopathological features compatible with atrophic gastritis and performed no more than three years before the patient inclusion date.

Exclusion criteria were a history of digestive tract surgery, except for cholecystectomy; suspected or current pregnancy; possibility of getting pregnant because of the inadequate use of contraceptive methods; presence of conditions associated with increased gastric acid secretion, such as Zollinger-Ellison syndrome; anatomical alterations in the nasal fossae impairing the passage of the catheter for prolonged esophageal pH monitoring; presence of complicated forms of GERD including Barrett's esophagus and peptic stenosis of the esophagus or presence of pyloric stenosis.

Upper Gastrointestinal Endoscopy

Upper gastrointestinal endoscopy was performed using an Olympus GIF-XQ 140 video endoscope (Olympus, America Inc., http://www.olympusamerica.com). During the procedure, the presence or absence of hiatal hernia and the severity of the esophagitis were evaluated. Hiatal hernia was diagnosed when the distance between the crural impression and the gastroesophageal junction was 2 cm or more.[7] The erosive esophagitis was graded according to Los Angeles classification.[8] Gastric biopsy samples were obtained using standard pinch-biopsy forceps. Antral and fundic biopsy specimens were systematically collected as follows: two from the mid-antrum, about 2 cm prepyloric from the anterior and posterior wall and two from the mid-body, about 5 cm distal of the gastroesophageal junction from the anterior and posterior body wall. Biopsy specimens were placed in 10% formalin and then embedded in paraffin blocks. Five-

micron sections were cut and hematoxylin and eosin stained and examined by an expert gastrointestinal pathologist. The diagnoses of chronic atrophic gastritis was based on the full spectrum of the updated Sydney System scores.[9]

^{13}C urea Breath Test

The patients included in the study were initially instructed regarding the discontinuation of any gastric antisecretory drug for at least 10 days (washout period), with the use of anti-acid drugs being permitted for symptom relief. After this period, a breath test with carbon-13-labeled urea was carried out to determine the possible presence of *H. pylori* infection. After an overnight fast of at least 8 hours, a CO_2 sample was collected from air expired into a 1.3-liter balloon for control. Next, the patient ingested 75 mg of carbon-13-labeled urea dissolved in 200 ml of natural orange juice, without the addition of water or sugar. After 30 minutes, a new sample of exhaled air was collected. Readings were made with an infrared analyzer (IRIS infrared isotope analyzer, Wagner Analysen Techinik, Bremen, Germany, http://www.wagner-bremen.de).

The results were obtained on the basis of absolute delta per 1000 or DOB, "delta over base", which indicates the modification of the $^{13}CO_2/^{12}CO_2$ ratio by the metabolic activity induced by the administration of labeled urea. DOB [0/00] values above four were considered positive, as previously validated by us.[10]

Study Medication

After confirmation of a negative UBT result, indicating the absence of *H. pylori* infection, patients were randomized according to the order of inclusion in the study to receive 20 mg of one of the following types of compounded or manufactured omeprazole:

- group A: omeprazole compounded by pharmacy A;
- group B: generic omeprazole;
- group C: omeprazole compounded by pharmacy B;
- group D: non-original omeprazole;
- group E: omeprazole compounded by pharmacy C; or
- group F: original omeprazole.

Non-original omeprazole and generic omeprazole were chosen by drawing lots among brands available on the Brazilian market identified in the 2007/2008 edition of the Dictionary of Pharmaceutical Specialties.[11] Compounded omeprazole was chosen by drawing lots from 20 compounding pharmacies identified in the 2006/2007 consumer telephone list of Belo Horizonte.[12] All drugs used in the study were bought in drug stores and magistral pharmacies, in which involved staff didn't know about the current study.

Five patients were randomized into each group so that at the end of the study half the patients (n=15) used compounded omeprazole and the remaining patients used manufactured omeprazole (generic, non-original or original). Patients were included in the study according to consecutive numeration, which defined the group of medication offered to the participants:

- patients included with numbers 1, 7, 13, 19, 25: group A medication;
- patients included with numbers 2, 8, 14, 20, 26: group B medication;
- patients included with numbers 3, 9, 15, 21, 27: group C medication;
- patients included with numbers 4, 10, 16, 22, 28: group D medication;
- patients included with numbers 5, 11, 17, 23, 29: group E medication; and
- patients included with numbers 6, 12, 18, 24, 30: group F medication.

To maintain their original characteristics, the study drugs were not removed from their original package. The drug expiration dates defined by the manufacturer and compounding pharmacies were respected. Patients were asked to ingest the drug 15 to 30 min before breakfast and treatment compliance was evaluated based on the diary kept by the participants.

Prolonged Esophageal and Intragastric pH Monitoring

The patients were submitted to esophageal and intragastric pH monitoring after a minimum period of seven days of omeprazole use. An esophageal pH meter from Sigma Instrumentos Ltda, Brazil (http://www.sigmainstrumentos.com.br) was used for the exam.. First, to guarantee correct placement of the pH probe, manometry was performed for

localization of the lower esophageal sphincter using the station pull-through technique (Sigma Instrumentos Ltda.). After calibration in buffer solutions with a pH of 7.01 and 1.01, the catheter, with two pH sensors positioned 15 cm apart, was placed 10 cm below the lower esophageal sphincter. Thus, the pH sensors were located 5 cm above and 10 cm below the lower esophageal sphincter. The patients were asked to fill out a diary in which they recorded periods of lying down, intervals between meals, time of omeprazole ingestion, and symptoms experienced during the exam.

Statistical Analysis

The results were analyzed statistically by the Student t-test and chi-square test for variables showing a normal distribution and by the Mann-Whitney test when no normal distribution was observed. A p value of less than 0.05 was considered to be significant.

RESULTS

Thirty-four patients were initially selected. Three of these patients (one from group A, one from group C and one from group E) were not included because they refused to undergo prolonged esophageal pH monitoring. Of the remaining 31 patients included in the study, one was excluded because of a positive UBT result. Thus, 30 patients concluded the study. The mean duration of pH monitoring was 23.8 hours (range: 22.3 to 24.0 hours). For analysis of the results, two groups of patients were compared, one using compounded omeprazole and one using manufactured omeprazole. Table 1 summarizes the demographic characteristics of the participants. Approximately two-thirds of the patients were females. Recurrence of symptoms of heartburn and regurgitation during the washout period was observed in 83.3% of the patients. The two groups were also similar in terms of age. Table 2 shows the esophageal alterations observed upon endoscopy performed in all participants at the time of diagnosis of GERD. Eighteen of the participants presented mild erosive esophagitis (Los Angeles grade A or B) upon baseline examination and 12 showed an intact esophageal mucosa. There was no difference in the proportion of patients with erosive esophagitis and hiatal hernia between the two groups.

TABLE 1 Demographic characteristics of the study participants

Characteristic	Total (n = 30)	Compounded group (n = 15)	Manufactured group (n = 15)	p value
Gender (male/female)	11/19	4/11	7/8	0.256*
Median age (years) (Q1 – Q3)	55.0 (45.0 – 66.5)	58.0 (44.0 – 65.0)	52.0 (47.0 – 71.0)	0.380 x

Q1 = 1st quartile; Q3 = 3rd quartile; * = chi-square test; x = Student t-test

TABLE 2 Esophageal alterations observed in the participants by upper digestive endoscopy performed at the time of diagnosis of GERD

Endoscopic alterations	Total (n = 30)	Compounded group (n = 15)	Manufactured group (n = 15)	p value
Erosive esophagitis/intact esophageal mucosa	18/12	7/8	11/4	0.136*
Hiatal hernia (present/absent)	22/8	10/5	12/3	0.409*

* = chi-square test

Table 3 illustrates the intragastric pH monitoring results obtained for the patients during omeprazole use. The values obtained showed a log-normal distribution, a fact that permitted the use of a parametric test for comparison of the findings between the two groups. Although a parametric test was used which permits the detection of small differences, similar results were obtained for the two groups.

Analysis of the results of esophageal pH monitoring during omeprazole use showed the absence of esophageal acid exposure in 40% of the patients who received the compounded drug and in 33.3% of the patients who used the manufactured drug. Abnormal acid exposure (percentage of total time of esophageal pH <4 greater than 4.2%) was observed in 25% of the participants of each group.

Table 4 illustrates the esophageal pH monitoring results (total time and time in supine and orthostatic positions) obtained for the participants, with no significant difference observed between the two groups.

TABLE 3 Comparison of the percentage of total time, time in the supine position and time in the orthostatic position of intragastric pH <4 between patients using compounded and manufactured omeprazole

Time pH <4	Total (n = 30)	Compounded group (n = 15)	Manufactured group (n = 15)	p value
Total time	41.6% (28.0% – 57.8%)	36.7% (25.7% – 57.5%)	47.7% (28.3% – 58.6%)	0.693 *
Orthostatic position	29.5% (13.2% – 48.9%)	30.1% (12.0% – 49.4%)	28.8% (13.4% – 48.7%)	0.881 *
Supine position	53.7% (41.7% – 72.1%)	49.6% (36.5% – 67.6%)	55.2% (44.3% – 75.6%)	0.694 *

Results are reported as median (1st quartile – 3rd quartile range). * = Student t-test

TABLE 4 Comparison of the percentage of total time, time in the supine position and time in the orthostatic position of esophageal pH <4 between patients using compounded and manufactured omeprazole

Time pH<4	Total (n = 30)	Compounded group (n = 15)	Manufactured group (n = 15)	p value
Total time	0.2% (0.0% – 4.4%)	0.1% (0.0% – 4.2%)	0.4% (0.0% – 4.9%)	0.372 *
Orthostatic position	0.15% (0.0% – 1.4%)	0.1% (0.0% – 2.5%)	0.3% (0.0% – 1.1%)	0.561 *
Supine position	0.0% (0.0% – 3.1%)	0.0% (0.0% – 2.3%)	0.0% (0.0% – 11.0%)	0.868 *

Results are reported as median (1st quartile – 3rd quartile range). * = Mann-Whitney

DISCUSSION

Manufactured drugs are found on the market in three forms. The original drug is the first one authorized for commercialization based on documents confirming its efficacy, safety and quality recognized by a sanitary authority. In general, an original drug is commercialized for an average period of 20 years by the pharmaceutical company that developed it and holds its patent. The non-original drug shares the same active ingredients, concentrations, route of administration, posology and therapeutic indications with the original drug and may only differ in terms of size, shape, packaging, expiration date, label and excipients. Non-original drugs are generally copies of the original substance with another fantasy name and can only be commercialized after the patent of the original product has expired. According to the "la revue prescrire" (1992)[13], in the case of drugs, any pharmaceutical specialty can be legally copied after patents on the active ingredient have expired through a so-called generic specialty that will be commercialized under the International Common Denomination (ICD) or a new brand name (considering that brand names are protected) by a manufacturer specialized (or not) in generic drugs. Studies confirming the bioequivalence to the original product are necessary for the production and commercialization of these formulations. In 1999, in Brazil, law number 9787 was published, which regulates generic drugs in Brazil that thus became a more accessible option for the low-income population. The generic drug has no commercial name, is sold based on the active ingredient and does not require investments in research for its development or marketing of the brand name, and is therefore of lower commercial cost than non-original drugs or the original substance.[14]

Another type of medication available is a compounded drug, which is produced on a smaller scale and by manipulation. In view of their individual scale of production, it is often impossible to submit these drugs to quality control tests and advanced technological processes commonly used by the industry (e.g., those guaranteeing the homogeneity of mixtures in solid medium). Thus, quality deficits related to the content of the active ingredient, quality of the raw material, content heterogeneity and bioavailability of the active ingredient may occur. In view of these limitations, there is consensus that this sector does not compete with the pharmaceutical industry or replace it, but only plays a complementary role.[15]

The peculiarities of medications produced by magistral pharmacies render their regulation by sanitary organs a complex process, which have given priority to the control of the manipulation of substances with a low therapeutic index, i.e., those that show a narrow safety margin and whose therapeutic dose is close to the toxic dose.[16] In Brazil, the use of compounded drugs, including omeprazole, by the population, is becoming increasingly more common since their cost is much lower than that of manufactured drugs. In view of their characteristics, clinical trials using compounded formulations are scarce[17,18]

To our knowledge, this is the first study comparing the antisecretory activity of manufactured (original and non-original) and compounded omeprazole formulations, randomly chosen among those available on the national market, using prolonged esophageal and intragastric pH monitoring. Prospective and controlled clinical trials have demonstrated a significant correlation between gastric acid suppression and healing of esophagitis; with this method thus, becoming relevant and clinically useful for the evaluation of the efficacy of drugs used for the treatment of reflux esophagitis.[19,20] We observed no significant differences in the percentage of total time, time in the supine position and time in the orthostatic position of intragastric pH <4 or in the presence of abnormal esophageal acid exposure between patients using compounded and manufactured omeprazole.

Variables that may potentiate the antisecretory action of PPI and thus, compromise the results of the study were carefully monitored. Infection with *H. pylori* may potentiate both the nocturnal and daytime antisecretory action of PPI[21]. It has been speculated that the production of ammonia by the bacterium, stimulated by a higher intragastric pH as a result of the antisecretory action of PPI, might be responsible for the better response to these drugs at night, when gastric acid production is reduced because of the absence of a

food stimulus.[22] In contrast, during the day, the production of ammonia is insufficient to affect intragastric pH since the human stomach produces large amounts of hydrochloric acid stimulated by the ingestion of meals. Thus, during the day, infection with *H. pylori* would potentiate the antisecretory action of PPI by reducing the gastric acid secretory response. In addition, *H. pylori* may interfere with gastric acid secretion by affecting the oxynthic mucosa of the body, causing hypochlorhydria[23], and by increasing the production of interleukin 1ß, which inhibits enterochromaffin-like cells.[24] It should be emphasized that this potentiation of the antiacid effect of PPI triggered by infection with *H. pylori* is normalized after erradication of the bacterium.[22,25] In the present study, patients infected with *H. pylori* and those with endoscopic and/or histological evidence of gastric atrophy were excluded.

We observed no difference in the time of esophageal acid exposure between the groups evaluated. The control of esophageal acid exposure is a determinant factor for symptom relief and healing of esophageal lesions secondary to GERD.[26] Factors that may influence the intensity of esophageal acid exposure include the presence of hiatal hernia, the intensity of esophagitis and patient gender. Banki et al[27], comparing risk factors for the development of GERD between men and women, observed that, although the frequency of typical symptoms of esophagitis was similar in the two genders, women presented lower esophageal acid exposure and a lower incidence of hiatal hernia and defective lower esophageal sphincter than men. The presence of hiatal hernia is an independent risk factor for the development of GERD, probably by prolonging the time of contact between the refluxate and the esophageal mucosa.[28-30] In the present study, the prevalence of hiatal hernia and its proportion among men and women were similar in the groups studied. The severity of the esophageal form of GERD also interferes with the degree of esophageal acid exposure. Esophageal acid exposure has been shown to be higher in patients with the complicated forms of GERD, mainly Barrett's esophagus, than in patients with uncomplicated esophagitis.[31,32] Up to 70% of patients with typical symptoms of heartburn and/or regurgitation have no endoscopic evidence of esophagitis and Barrett's esophagus. This group of patients has been described as having non-erosive reflux disease (NERD).[33] NERD patients usually have less esophageal acid exposure and incomplete symptom relief with PPI than patients with erosive esophagitis.[34,35] Lind et al[36], studying patients with heartburn and negative endoscopy observed that the highest rate of symptom control with PPI was obtained on those with greatest esophageal acid exposure. We only included patients with typical symptoms of GERD, which responded satisfactorily to previous omeprazole administration, and nevertheless the prevalence of patients with mild erosive esophagitis and NERD mucosa was similar in the groups analyzed.

Our study has some limitations. Since any study involving invasive work-up such as pH monitoring in the esophagus and stomach causes discomfort, the size of the sample is kept to a minimum. Another aspect refers to the use of different omeprazole formulations available on the market, both manufactured and compounded drugs, considering the difficulty in reproducing the results of studies employing the latter formulations. In fact, the present investigation was a pilot study initially evaluating large differences between medications commonly found on the national market.

Our results showed that the omeprazole medications studied (compounded and manufactured) resulted in similar control of gastric acid secretion and esophageal acid exposure in patients with mild forms of GERD. Further studies involving a larger number of patients and the implantation of regulatory measures able to guarantee an effective and safe quality control for the production of compounded medications are necessary to validate their use for an important part of the Brazilian population that has no access to manufactured antisecretory drugs because of economic limitations.

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