Effects of a single low dose of ranitidine and effervescent antacids on intragastric acidity in healthy volunteers

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Summary

Introduction/aims: *We hypothesized that a combination of an effervescent antacid and ranitidine could allow immediate and long-lasting increase intragastric acidity. Our aim was to determine the effect of the combined intake of both, of a low dose ranitidine (OTC) and 5g of antacid on gastric pH.* ***Material and methods:*** *Twenty healthy Helicobacter pylori negative volunteers were enrolled. The study consisted in a fasting 6-hour gastric ph-metric procedure performed in two different periods: baseline (1-hour before drug) and post-drug (5-hours) after oral administration of a single dose of ranitidine (75 mg) plus 5 g of a commercial composed alkaline (sodium bicarbonate, citric acid, sodium carbonate).* ***Results:*** *While two subjects did not complete the pH-metry analysis due to technical reasons, 18 volunteers were finally assessed. Baseline intragastric pH (1.3±0.1) (mean±SD) rose significantly after administration of the drug (mean pH value for the whole period: 5.1±0.3; p<0.00001). The pH increased after administration of the study combination and values higher than pH 3 and pH 4 were reached immediately (median time: 27 sec, range: 0-189 and 54 sec, range 27-3,600 sec, respectively). Gastric pH was initially maintained above 4 for 23.0±5 minutes. The mean time lapsed with pH<4 during the post-drug period was 96±17 min (32% of the total time).* ***Conclusion:*** *Our study confirms the fast and persistent effect produced by the administration of a combination of antacid salts plus low dose of ranitidine. We suggest that the given combination could be effective, fast and safe for sporadic pyrosis or mild grastroesophageal reflux symptoms.*

Key words: *Ranitidine, antacids, gastric acidity.*

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Efectos de bajas dosis de ranitidina y antiácidos efervescentes sobre la acidez intragástrica en voluntarios sanos

Resumen

Introducción/objetivos: *la combinación de un antiácido efervescente y ranitidina podría brindar un descenso inmediato y prolongado de la acidez intragástrica. Nuestro objetivo fue determinar el efecto de la ingesta conjunta de ambos (75 mg de ranitidina y 5 g de antiácidos) sobre el pH gástrico.* ***Material y métodos:*** *se incluyeron 20 voluntarios sanos, con anticuerpos anti-Helicobacter pylori negativos. Se realizó, en condiciones de ayuno, una pH-metría gástrica de 6 horas en dos períodos: basal (1 hora antes del medicamento) y post-droga (5 horas) luego de la administración oral de una dosis única de ranitidina (75 mg) + 5 g de antiácidos efervescentes (bicarbonato sódico, ácido cítrico, carbonato sódico).* ***Resultados:*** *dado que dos pacientes no completaron el estudio de pH por razones técnicas, se analizaron los resultados de 18 voluntarios. El pH intragástrico basal fue de 1.33±0.12 (promedio ± DS) y se elevó a 5.1±0.3 como promedio de todo el período post-droga (p<0.00001). El incremento de pH fue inmediato; así los valores de pH=3 y pH=4 fueron alcanzados en 27 seg, rango: 0-189 y 54 seg, rango 27-3.600, respectivamente (mediana, rango). El pH se mantuvo inicialmente por encima de 4 durante 23.0±5 minutos. El tiempo con pH < 4 durante las 5 horas post-droga fue de 96± 17 minutos (32% del tiempo total).* ***Conclusión:*** *nuestro estudio confirma el*

efecto rápido y persistente determinado por la combinación de sales antiácidas y bajas dosis de ranitidina. De este modo esta asociación podría ser efectiva, rápida y segura frente a pirosis esporádica o síntomas de reflujo gastro-esofágico leve.

Palabras clave: *Ranitidina, antiácidos, acidez gástrica.*

It has been estimated that many "healthy" individuals (30% of adults in the United States) may experience pyrosis or similar symptoms on a monthly basis. Furthermore, over 20% of the population suffers from acidity at least once a day.[1] Patients presenting sporadic acidity episodes, usually linked to alcohol consumption or voluminous meals, should be distinguished from those for whom a true gastroesophageal reflux (GER) is detected. In this context, Katz and Castell[2] have also suggested a distinction between GER in the following degrees: mild (< 2 episodes a week), moderate (>2 episodes a week) and severe (1 episode a day). Many patients who suffer sporadic acidity episodes or mild GER self medicate with antacids or resort to techniques aimed at decreasing gastric acidity or at increasing the pH of the refluxed material.

Rapidness and efficacy of action are considered of utmost importance in alleviating GER symptoms. In this setting, antacids are one of the most widely used self-prescribed drugs.[3] These are made up of calcium carbonate, magnesium and aluminum salts in different combinations. Each of these salts has pharmacological characteristics that are important when determining the type of product that should be used in each case. The effect of antacids on the stomach is due to the partial neutralization of hydrochloric acid and to the inhibition of proteolytic enzymes, such as pepsin, which determines a fast decrease in acidity within 30 minutes post-administration. Although relief comes around 5-15 minutes after,[4] its duration is relatively short (1-3 hours). Thus, it is assumed that, in order to achieve an adequate symptom control with these drugs, multiple doses are required through the day. It should be highlighted that antacids are inexpensive and can be purchased over the counter although they are not free of side effects"

On the other hand, due to their well-documented efficacy and safety, the low dose administration (at half the usual dose) of H_2-receptor antagonist drugs (ranitidine) has been used for treating pyrosis and these drugs are currently over the counter medications. When compared to antacids, the symptomatic relief in those subjects receiving ranitidine presents some specific characteristics; it occurs later but it has a longer term effect on esophagus acid exposure and gastric acidity. Thus, studying a population made up of 1620 patients, Cicciola et al[5] have shown that ranitidine (75mg) was more clinically effective than placebo in relieving sporadic acidity and reducing antacid intake. This treatment was generally well tolerated and adverse effects are not more frequent than those determined by placebo. Galmiche et al[6] reported that on-demand use of ranitidine 75 mg was significantly more effective than placebo in determining symptomatic global relief in the study of 1336 patients with acidity episodes. Finally, Pappa et al[7] clearly established that ranitidine 75 mg is effective in completely preventing or decreasing acidity when administered 30 minutes before a meal.

If the immediate effect of effervescent antacids were combined with the long-lasting systemic response of H_2-receptor antagonists (ranitidine), it could be argued that we would obtain a medication than can offer a fast decrease in intragastric acidity and at the same time a therapeutic effect that would extend longer. The aim of this study was to determine the therapeutic effect of taking a single dose of ranitidine (75 mg) and 5g of a commercial combination of effervescent antacids on intragastric acidity in the 5 hours following administration of study drugs in fasting conditions.

Material and methods

Material

The study enrolled 35 adult healthy volunteers (30 women, mean age: 35 years old; range: 22-49) who signed written informed consent. Subjects were excluded if they were: 1- pregnant women or having positive pregnancy tests, 2- breastfeeding women, 3- *Helicobacter pylori* infection, 4- past history of gastrointestinal or extradigestive disorders, 5- alarm signs or symptoms, 6- renal or hepatic failure, 7- consumption of medications including administration of antacids or drugs that may affect gastric secretion or esophageal motility in the week prior to the study, 8- alcohol abuse, 9- patients undergoing treatment with low-sodium diet and, 10- known or suspected intolerance or hypersensitivity to ranitidine or effervescent antacids (or to related compounds), or to any of their excipients.

Methods

a-Initial clinical interview and serology

Controls were initially assessed in terms of the clinical history, considering all relevant information, whether medical or surgical, including allergies or hypersensitivity to drugs and the administration of all concomitant drugs. In the week after the first interview, human chorionic gonadotrophin blood assessments were determined, as well as tested for anti-*H.p.* antibodies (IgG and IgA) through a commercial assay (ELISA).

b- Intragastric *pH* monitoring

The intragastric *pH* test was performed one week after the initial interview. All participants were asked to visit the clinic in a fasting state from at least the prior midnight and after warning them to abstain from drinking alcohol and caffeine-containing beverages (tea, coffee, chocolate, cola soda drinks) for 24 hours before the study.

At 8:00 am, an antimony probe was placed in the volunteers gastric cavity with the aim of measuring intragastric pH. The catheter was always intranasally inserted by the same operator (R.A.), and its positioning in the stomach was confirmed by the methodology known as "*pH* fall",[8] which consist in the identification of the abrupt *pH* fall that occurs when passing from the esophageal lumen (*pH*>6) to the gastric cavity (*pH*= 1 to 2). From the site at which this drastic decline was identified, the catheter was further introduced 5 cm. (approximately 55 cm. from the nostril). After ensuring correct placement of the electrode, the latter was affixed to the face with adhesive tape, after which the data were recorded.

Intra-gastric *pH* was measured for 6 hours, divided in 2 periods: a- **Baseline:** during the first 60 minutes and before the administration of the study drug, administered as a single dose and single take, and b- **Post-drug:** during the 5 hours after its administration of the study drug combination. The effervescent antacid was dissolved in 150 ml of water, and its administration together with ranitidine was supervised by study personnel (R.A. and E.S). Subjects were not allowed to drink or eat at any time of the 6 hours *pH* measurements. Patients were not allowed to smoke either.

Technical aspects of the pH-metry

The *pH*-metric study was performed with monocrystalline antimony electrodes, as well as with a reference dermal electrode placed transnasally and connected to a recorder (Medtronic Digitrapper pH recorder; Minneapolis, MN, USA). Prior each study, the *pH* probes were calibrated taking pH 1 and 7 solutions as base. Furthermore, catheters were appropriately rinsed before use under strict antiseptic measures, including immersion in 2% glutaraldehyde. Measurements were recorded every 6 seconds during the 6 hours of the study. As with the other commercially available programs, the software analyzed the *pH* data by means of different variables: start time and duration of the action of the study drugs (period in which *pH*>4 is achieved); total percentage of time with *pH*>4.

c- Study drug

A single oral dose of ranitidine (75 mg) (Zantac®; GSK; Spain) was administered, plus a 5 g dose of white crystalline "powder" (ENO®; GSK; Argentina) containing: sodium bicarbonate (46.13 g/100 g of powder); citric acid (43.87 g%); sodium carbonate (10g%).

Assessment of results

Given that a *pH*>4 has been recommended as threshold for the relief of pyrosis determined by GER disease,[2] the time percentage with *pH* values >4 was used as the primary endpoint in the statistical analysis. In addition, another efficacy endpoint was the time in reaching a *pH* of 4 after the administration of the study drugs.

Statistical methods, study design and ethical aspects

The results are expressed as mean values and standard deviations (SD), or median and range, according to data distribution. T-test or Mann-Whitney tests were used to determine statistical differences when applicable. A confidence level of 0.05 was considered significant, and a value of 0.01 as highly significant. The design of the study was an open one, comparing basal and post-drug perfomed at a single site and using single doses of the study drugs. This study was perfomed in total compliance with the principles of the Declaration of Helsinki (1989)[9] and international "Good Clinical Practice" guidelines,[10] and subjects signed written informed consents. The protocol was approved by the local Teaching and Research Committee.

Results

Recruited population

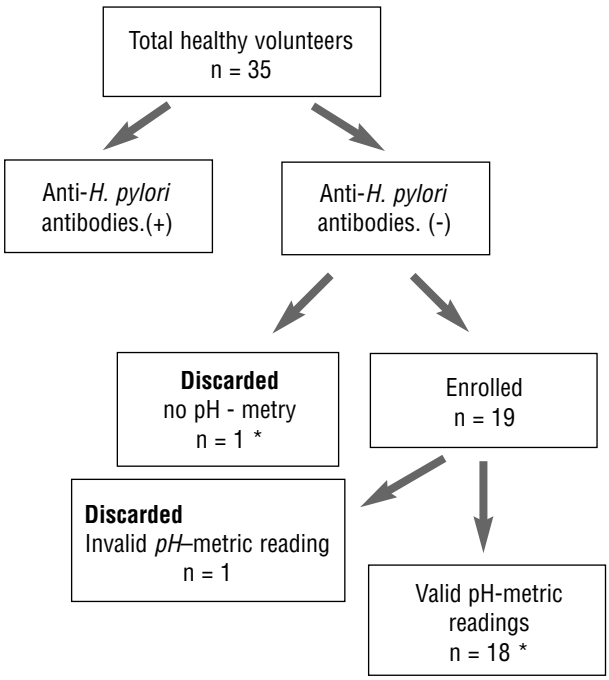
While 35 healthy volunteers were enrolled into the

study, 15 of them had positive anti-*Helicobacter pylori* type IgG antibodies, and were thus excluded (table 1). Thus, 20 subjects participated in the study. Two patients failed to complete the *pH*-metric analysis for different reasons: 1- the catheter could not be inserted in one case since the probe did not pass through the upper esophageal sphincter, despite the volunteer's willingness and the repeated procedures. 2- basal *pH* assessments in another volunteer were quickly found to be over 4, which did not allow to have adequate reference values. Such circumstance was probably due to the presence of alkaline duodenal reflux. Finally, the per protocol analysis allowed us to assess the *pH*-metric results obtained in 18 volunteers (17 women, mean age 33 years old; range 22-42), seven of whom were usual smokers (figure 1).

Table 1. Demographic data. *Demographic characteristics of the screened volunteers and of the subjects who were finally enrolled (who resulted H. Pylori -ve).*

	Enrolled volunteers	Hp -ve subjects
n =	35	20
Mean age (years) X Range	35 22 – 49	33 22– 42
Gender (F / M)	30/5	17/1
Current smokers	14	7
Alcohol consumption	3	-

Figure 1. Flow chart of the overall population. *The enrolment characteristics of healthy volunteers are detailed in terms of the serological results of anti-H. pylori antibodies.* Due to technical difficulties, the pH-metry was not performed in one healthy volunteer, and the pH-metric study was not finished in another one.*



pH-metric assessments

Basal *pH*. The mean intragastric *pH* for the overall population determine during the first 1-hour determination before receiving the study drug was 1.33±0.12 (±SD). Such finding has been highly constant in the different subjects and throughout the whole assessment period, as can be observed through the reduced SD of the measurement (figure 2).

Post-drug administration *pH* (Alkalines + 75 mg of ranitidine). Based on pharmacodynamic reasons, our analysis arbitrarily considered that the first hour following the intake of the test drugs consisted in changes brought about by the alkaline salts. For the same reasons, we consider that subsequent *ph*-metric effects, and those that take place in the following four hours, are attributable to the ranitidine effect.

Following the administration of the study drugs *pH* increased immediately. The maximum *pH* peaks achieved by alkalines and ranitidine were 6.3±1.0 and 7.7±0.4 ($p<0.0001$), respectively (figure 3). Thus, *pH* 3 and *pH* 4 values were achieved immediately (medians: 27 sec., range: 0-189; 54 sec, 27-3,600, respectively) from the basal *pH*. One of the participants did not experience a pH increase in the first hour, which explains the dispersion in the obtained data. After reaching a value of *pH* 4, this was maintained above it for a period of 23.0±5.0 min. If we consider the first 60 minutes after taking the study drugs (period in which the changes would be attributable to the antacid salts), the mean duration of *pH*<4 for the overall population was 28.4±5 min, which represents 46.3% of the time.

Compared with the baseline determination, the mean intragastric *pH* recorded in the overall period (5 hs post study drug) showed a highly significant increase to 5.1±0.3 ($p<0.00001$) (figure 2). Figure 4

Figure 2. *Median, SD and range for pH at the basal (one hour determination) and post-drug periods (comprises the mean of 5 assessment hours) (p<0.00001).*

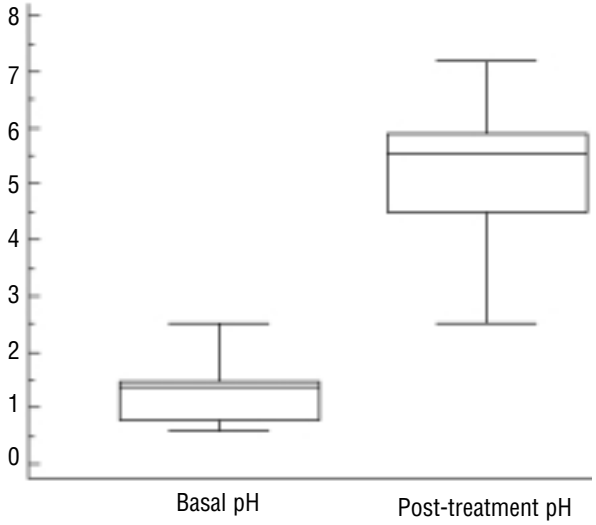
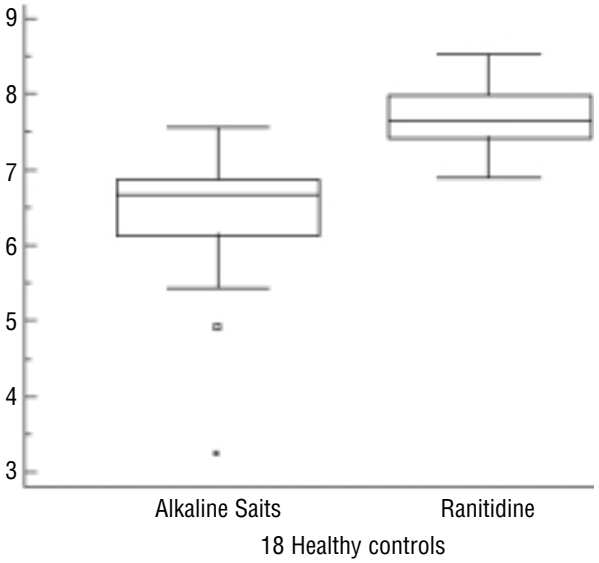


Figure 3. *Mean value, SD and range for the maximum pH peak obtained comparing both, the first hour post-drug administration (alkaline salts effect) and he last four hours (ranitidine effect) (p<0.01).*



depicts the time course mean *pH* value recorded both at the baseline hour (1.33±3.8) and at each hour (1st hour: 4.1±3.8; 2nd hour: 5.5±6.1; 3rd hour: 5.9±6.4; 4th hour: 5.3±5.9 and 5th hour: 4.6±4.6) after the administration of the study drug (p<0.00001 for all comparisons with the baseline determination). The only *pH* assessments that presented statistically significant differences with respect to other values were those corresponding to the basal *pH* for each of the 5 post-drug hours analyzed (p< 0.00001).

Finally, the time in which *pH* remained below 4 during the 5-hour post-drug was 96±17 min, representing 32% of the overall period. Figure 5 shows the hourly progress (from the baseline to the end of the recorded period) in percentage of time with a *pH* below 4. The figure shows that while the acid enviroment was present in 98.9% of the time in the baseline period, a significant decrement was detected after the intake of the study combination. Thus, acidity was reduced in 46.3% of the 1st hour (atributable to alkaline salts) and in each of the 4 hours after that (24.1%, 18.4%, 32.7% and 44.9% in the 2nd, 3rd, 4th, and 5th hour, respectively) (effect attributable to ranitidine). The analysis of the results with respect to the smoking habit did not show statistically significant differences in all the variables analyzed (p=NS).

Adverse effects. The study drug was well tolerated. No clinical adverse effects were observed in any of the participants. None of the participants had to be withdrawn from the research protocol due to intolerance to the study components.

Figure 4. *Mean pH at different periods: basal and post-drug administration (five 1-hour periods) in the 18 healthy volunteers. (Basal vs. treatment p<0.0000).*

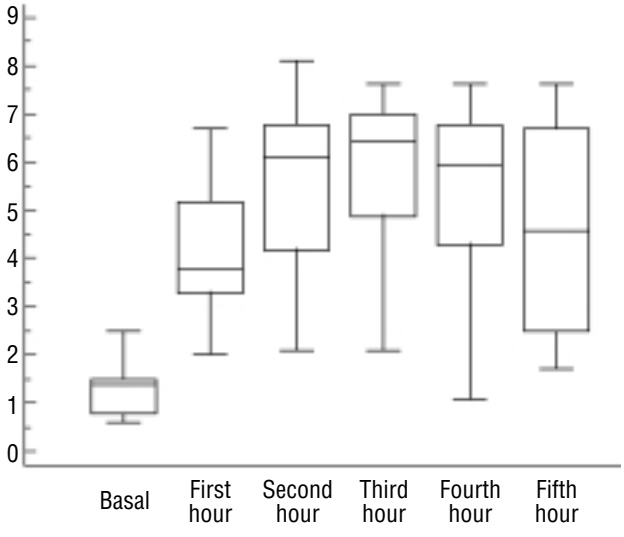
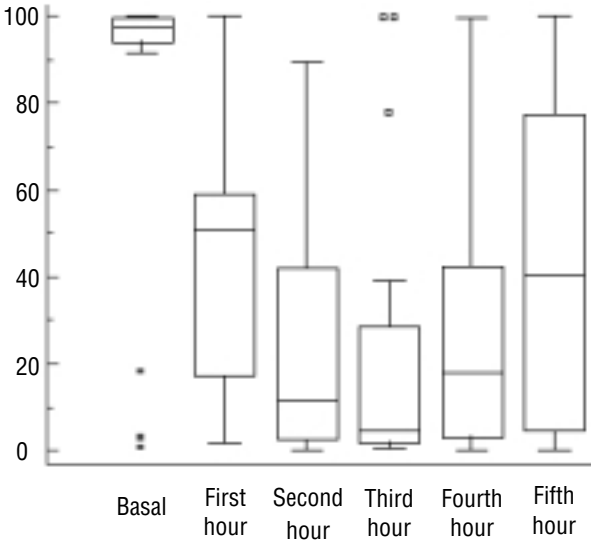


Figure 5. *Percentage of time with a pH below 4 for each study period. (Basal vs. post-treatment hours p<0.00001)*



Discussion

The fact that pyrosis and other gastric acid-related symptoms are generally associated with reflux of gastric content to the esophagus suggests that treatments aiming to reduce acid secretion and increasing *pH* of the refluxed material should be very effective in alleviating symptoms. Thus, the use of alkaline salts, H_2 receptor antagonists and proton pump inhibitors (PPI) are options for improving symptoms. However, the last two are preferred due to the fact that both produce a prolonged inhibition of basal and stimulated gastric acid secretion and, therefore, makes less aggressive the refluxed material. Although PPI are the most effective drugs, the effect has also been observed with drugs such as ranitidine, both at usual doses (150-300 mg a day)[11] and in low doses (75 mg).[5-7] Epidemiological studies suggest that most patients with symptoms potentially due to reflux are not clinically affected on a daily bases and, likely, the majority of them present symptoms even less frequently. Therefore, the continue use of PPI in patients with sporadic symptoms is not considered the best therapeutic strategy. In this context, administration of H_2 blockers seems adequate. However, the use of ranitidine has a latency period which exceeds 30 minutes and its maximum effect is produced after the first hour following administration. Therefore, based on the rapid action of alkaline salts, it is very interesting to analyze the value of adding the latter in combination with ranitidine with the aim of achieving a double effect, a fast action (due to alkaline agents) and a more prolonged relief of the symptoms (due to the use of ranitidine). Furthermore, many patients who experience sporadic acidity episodes or mild GERD do not consult a physician and self-prescribe antacids or over the counter (OTC) H_2 blockers available in the United Kingdom since 1994.[12] Up to date, no significant data have shown that these individuals may present a higher risk of developing complications due to the GERD;[13] thus, this practice can be considered as having appropriate safety levels.

The present study was designed in order to investigate the response of the intragastric *pH* induced by a combination of antacid salts and low dose ranitidine (75 mg). It should be highlighted that this study was performed in healthy volunteers in fasting conditions. During this period, symptoms are most significant, which means that antacid self-prescription is more frequent. In this sense, it should be mentioned that the neutralizing effect of food intake normally produces an increase in gastric *pH*, with the subsequent relief of dyspeptic disturbances and a decrease in the need of over the counter drugs.[14]

It is well-known that the infection by *Hp* can determine changes in intragastric pH levels.[15] In this context, a negative specific serology (serum antibodies for *Hp*) was considered a determining condition for the enrollment of volunteers and excluding influence of the bacteria on the effect of the study drugs. The therapeutic effect of the drugs used in the treatment of GERD symptoms when taken irregularly for alleviating gastric acid related discomfort should be analyzed in terms of the gap between intake and effect and duration. To attain fast symptom relief, it is crucial that gastric acid neutralization starts immediately after taking the drug.[16-17] Different antacid salts studied with this purpose have proved useful in increasing gastric *pH* in a few minutes, which quickly relieves symptoms.[3-4] Our results revealed a fast action starting immediately after administration of antacid salts plus a low dose ranitidine, evidenced by the immediate increase in intragastric *pH*. Since previous studies showed that changes in the pH after the administration of ranitidine become apparent latter than 60 minutes after administration,[4] we should consider that antacid salts included in this drug combination are responsible for the rapid *pH* increase. It should also be highlighted that the effect of the antacids administered would further accelerate its action (less than 1 minute) with respect to other similar substances previously studied. Thus, in an important study carried out by Netzer et al,[4] the use of calcium and magnesium carbonates showed a longer mean ti-

me for achieving *pH* over 4 (5.8 minutes).

The percentage of time with *pH* higher than 4 induced by a drug or a combination is another important index in the analysis of the response to drugs like the ones used in this study. Thus, GERD symptom control level correlates with the length of time during which a *pH* is maintained over that level, threshold after which gastric reflux peptic activity is abolished.[18-20] Netzer et al[4] reported that 75 mg of ranitidine increases the *pH* above 3 during 61.4% of the time.

In our study, the tested combination maintained *pH* above 4 for almost 70% of the time considering the 5-hour period after administration. This result could be attributed to the effect of the joint administration of antacid salts and ranitidine, and this likely related to the additional effect of alkaline drugs in the first hour after its administration.

It should be highlighted the absence of adverses effects.

In conclusion, the results of the present study confirm the rapid and long-lasting effect provided by the combination of antacid salts, which determine the immediate intragastric *pH* increase (in less than a minute), and ranitidine, responsible for the longer and sustained effect of increasing gastric *pH*. Thus, it could be speculated that, faced with mild GERD symptoms, this drug combination could be effective with a fast action and safe profile.

Disclosures

María Cecilia de los Santos and Javier Martinelli Massa are employees of Glaxo-Smith-Kline (GSK) Argentina. The remaining authors have no financial associations with GSK other than in this respect and receive no support other than that directly concerned with the conduct of the study. This study was funded in full by GSK.

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