

Regression of gastroesophageal reflux disease symptoms using dietary supplementation with melatonin, vitamins and aminoacids: comparison with omeprazole

Abstract: The prevalence of gastroesophageal reflux disease (GERD) is increasing. GERD is a chronic disease and its treatment is problematic. It may present with various symptoms including heartburn, regurgitation, dysphagia, coughing, hoarseness or chest pain. The aim of this study was to investigate if a dietary supplementation containing: melatonin, L-tryptophan, vitamin B6, folic acid, vitamin B12, methionine and betaine would help patients with GERD, and to compare the preparation with 20 mg omeprazole. Melatonin has known inhibitory activities on gastric acid secretion and nitric oxide biosynthesis. Nitric oxide has an important role in the transient lower esophageal sphincter relaxation (TLESR), which is a major mechanism of reflux in patients with GERD. Others biocompounds of the formula display anti-inflammatory and analgesic effects. A single blind randomized study was performed in which 176 patients underwent treatment using the supplement cited above (group A) and 175 received treatment of 20 mg omeprazole (group B). Symptoms were recorded in a diary and changes in severity of symptoms noted. All patients of the group A (100%) reported a complete regression of symptoms after 40 days of treatment. On the other hand, 115 subjects (65.7%) of the omeprazole reported regression of symptoms in the same period. There was statistically significant difference between the groups ($P < 0.05$). This formulation promotes regression of GERD symptoms with no significant side effects.

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Introduction

Gastroesophageal reflux disease (GERD) is the reflux of gastric contents into the esophagus and/or adjacent organs, with or without tissue damage [1]. The most prominent symptom is heartburn, with or without regurgitation of gastric contents into the mouth. GERD is a common condition, with an estimated 44% of the adult population in USA experiencing its symptoms monthly [2]. In Brazil, there is no national study done with adequate and specific statistical analysis [3].

Gastroesophageal reflux disease can be subdivided into several groups: (a) nonerosive GERD (NERD); (b) erosive GERD; (c) Barrett's esophagus with GERD-related complications. NERD has been defined as the presence of typical symptoms of GERD caused by intra-esophageal acid in the absence of visible esophageal mucosal injury [2]. It is estimated that up to 70% of patients with typical GERD symptoms in the Western Hemisphere have normal endoscopy [4].

Acid-suppressant drugs predominate in the treatment of GERD. Proton pump inhibitors (PPIs), such as omeprazole, esomeprazole (the S-enantiomer of omeprazole), lansoprazole and rabeprazole, are widely used for the treatment of GERD and they are also used in maintenance

therapy [5, 6]. PPIs are the first-line choice in both reflux esophagitis and nonerosive reflux disease (NERD). PPIs effectively inhibit the duration and extent of gastric acid secretion and provide more complete remission of the symptoms of heartburn than others forms of acid-suppressant therapy [7, 8]. However, the response to PPIs in patients with NERD is less efficacious when compared with patients with erosive GERD [2, 9].

Lansoprazole, omeprazole, esomeprazole, and rabeprazole have potentially serious adverse side effects. They abolish acid production so completely that serum gastrin levels rise. In rodents enterochromaffin-like cell tumors and carcinoid tumors have developed. It is not known whether these drugs are carcinogenic in humans by a similar mechanism [10, 11]. Moreover, bacterial overgrowth may develop in the stomach in the absence of acid. Bacterial metabolism of dietary nitrites may then lead to the production of N-nitroso compounds that are carcinogenic [10, 12]. This risk is not limited to chronic omeprazole treatment; it can theoretically occur with any effective long-term antacid regimen. Moreover, omeprazole appears to affect cytochrome P450. Although initial studies suggested an inhibitory effect, more recent studies indicate that omeprazole may induce the cytochrome P450 1A subfamily that is associated with activation of certain chemical

procarcinogens, such as polycyclic aromatic hydrocarbons [10].

To promote the regression of the pivotal symptoms of GERD/NERD (heartburn or acid regurgitation), a formulation with melatonin, vitamins and aminoacids, which has no significant side effects, was developed. This formulation is based on information accumulated by our research group [13–19] and those obtained from scientific literature based on the fact that melatonin has inhibitory actions on gastric acid secretion [20, 21] and on the biosynthesis of nitric oxide [21, 22]. As the supplement contains natural compounds found in foods, this formula presents fewer side effects than medications currently used in clinical medicine.

Materials and methods

Use of aminoacid and vitamin supplement

Biochemical materials [melatonin (6 mg), tryptophan (200 mg), vitamin B12 (50 µg), methionine (100 mg), vitamin B6 (25 mg), betaine (100 mg) and folic acid (10 mg)] were obtained from Galena (Campinas, SP, Brazil). The formulation was prepared by a trained pharmacist. Supplementation (melatonin, vitamins, and aminoacids) or 20 mg omeprazole were inserted into identical capsules to ensure a single-blind study. A set, containing 40 gelatin capsules, was used to treat one patient for 40 days (one capsule a day). Patients received a 40 days supply of medication. A total of 351 sets were prepared for use by 351 patients. This type of therapy was ongoing, with the dose of one gelatin capsule a day, which was sufficient to control symptoms of reflux and heartburn. Ambulatory 24-hr pH monitoring was not performed. The starting date of the therapy was recorded for each patient.

Patients and inclusion criteria

Patients with heartburn, regurgitation, dysphagia and chest pain were enrolled into this prospective, randomized, parallel-group comparative, single blind, single-center study. Heartburn was defined as ‘substernal burning sensation or pain’. A description of ‘a burning sensation behind the breastbone rising up to the throat or neck’ or a ‘burning pain or discomfort behind the breastbone rising up towards the neck’ was accepted as ‘heartburn’. Patients who described these symptoms as a burning, warm or acid sensation in the epigastrium, substernal area or both were also accepted as having ‘heartburn’. Regurgitation was defined as ‘food or fluid coming back up from the stomach’. Eructation was defined as ‘belching’.

To qualify for inclusion in the study, subjects had to have experienced at least one period of moderate-to-very severe heartburn or regurgitation in the past 7 days before treatment. All patients gave their fully informed written consent before entering the study.

Exclusion criteria

Patients with hepatitis, liver cirrhosis, or other serious concomitant illnesses were excluded from this study.

Symptom severity

Patients recorded the severity of GERD symptoms in a daily diary. Severity was graded on a five-point scale from none (0), mild (1), moderate (2), severe (3) and very severe (4) for each of the following symptoms: day-time heartburn, night-time heartburn, day-time regurgitation, and night-time regurgitation.

Other upper GI symptoms of belching (eructation), early satiety (the sensation of filling up quickly), bloating (feeling like I have a lot of gas in my belly), nausea and vomiting were also recorded on the five-point scale as explained above.

Symptom severity was scored according to the following scale: 0, no symptoms; 1, mild (symptoms are present occasionally and patients can continue with daily activities); 2, moderate (symptoms are present most of the time but patients can perform daily activities); 3, severe (symptoms are present continuously. The symptoms are severe and affect daily activities or patient cannot do things that they normally can); 4, very severe (symptoms are so severe that patients have to stay in bed and cannot perform activities that they normally could).

Outcome measures

The efficacy of treatment was the time taken (in days) for patients to achieve their first 24 h interval without any symptoms of heartburn or regurgitation [23]. Safety and tolerability were evaluated by recording adverse events for both groups.

Randomization

Patients who qualified were randomized: 176 patients received the supplement containing melatonin, vitamins and aminoacids (group A) and 175 patients received 20 mg omeprazole (group B). It was recommended that each patient take one capsule a day after the evening meal. No other medication was allowed.

Endoscopy

Endoscopies were performed by gastroenterologists, using a Fujinon EG 300 endoscope.

University Ethics Committee

The data were evaluated and approved by University Ethics Committee in August 2004. To protect intellectual property, a patent was registered. The study was conducted in accordance with the Declaration of Helsinki.

Statistical analysis

The results of treatment were evaluated with per-protocol (PP) analysis (which included only patients who completed the study) and intention-to-treat (ITT) analysis (which included also patients who did not complete the study). The demographic and clinical characteristics of the two groups (A and B) were compared by Chi-square test or Fisher's

exact test. The results of treatment were compared by Chi-square test. $P < 0.05$ was considered statistically significant.

Results

Patients

A total of 351 patients with heartburn entered the surveillance program between January 2001 and December 2005. Mean age at enrollment was 44 yr, with a range from 18 to 88 yr; 59.82% were women. The number of patients recruited per year increased over the course of the study as the practice grew; the median year of enrollment was 2003.

In terms of geographical area, the subjects are from 19 different cities and towns from five Brazilian states: 197 patients (56.12%) are from São Paulo, 148 (42.17%) from Minas Gerais, three (0.85%) from Paraná, two (0.57%) from Espírito Santo and one (0.29%) from Distrito Federal. Some of them are separated one another about of 2500 km. In terms of social class: 74 patients (21.09%) are rich, 172 (49%) are from middle class and 105 (29.91%) are poor. In terms of education: 124 (35.32%) have university degree [from these, 17 (4.84%) are university professors and scientists and two (0.56%) are physicians], 209 (59.54%) have high school, 17 (4.84%) have incomplete high school and one (0.3%) is illiterate.

The subjects were divided in two groups: it was allowed to 176 patients use the supplement, containing melatonin, aminoacids and vitamins described in this paper, during 40 days without using any other medication (even antacids) (group A) and, for comparison, the other half ($n = 175$ volunteers) used omeprazole (group B). So, there

Table 1. Baseline characteristics of patients enrolled in the current study

	Group A ($n = 176$)	Group B ($n = 175$)
Gender (M/F)	61/115	80/95
Age (yr) (S.D.)	43.68 (13.3)	44.26 (15.2)
Smoking	75 (42.6%)	88 (50.3%)
Alcohol abuse	8 (4.5%)	10 (5.7%)
Previous medication for reflux disease	32 (18.2%)	19 (10.8%)

Table 2. Healing rates of patients in the two treatment groups

	Group A ($n = 176$)	Group B ($n = 175$)	P -value	χ^2 -test
PP analysis (%)	176/176 (100)	115/173 (66.5)	0.001	70.766
ITT analysis (%)	176/176 (100)	115/175 (65.7)	0.001	72.785

Table 3. Adverse events during the treatments used in the current report

	Group A ($n = 176$)	Group B ($n = 175$)
Diarrhea	0 (0)	7 (4)
Headache	0 (0)	2 (1.1)
Hypertension	0 (0)	3 (1.7)
Somnolence	159 (90.3)	4 (2.3)

The value are given as n (%).

were significant differences in eradication rates between the two groups. The demographic and clinical characteristics of the 351 subjects in the two groups are shown in Table 1.

After finishing the 40 days of treatment, total regression of the symptoms (markedly improved) was observed in 100% of the subjects of the group A. They reported relief of the symptoms after 7 days taking the supplementation. These results indicate that GERD can be regressed with melatonin, vitamins and aminoacids of the formulation presented in this paper. Completed questionnaires about the adverse events and compliance were obtained from all the 351 patients. A total of 159 patients (90.3%) of group A related somnolence and sleep improvement.

A total of 115 patients of group B (65.7%) reported relief of the symptoms (markedly improved) after 9 days of treatment, four patients (2.3%) reported partial relief (slightly improved) and the remainder continued to feel all symptoms described 40 days before starting the treatment. Two patients (1.1%) of group B withdrew from the study because of persistent headache caused by omeprazole.

In terms of regression of all symptoms, there was a statistically significant difference between groups A and B: the active healing rate was 100% (176/176) in group A (subjects who used supplementation of melatonin, amino-

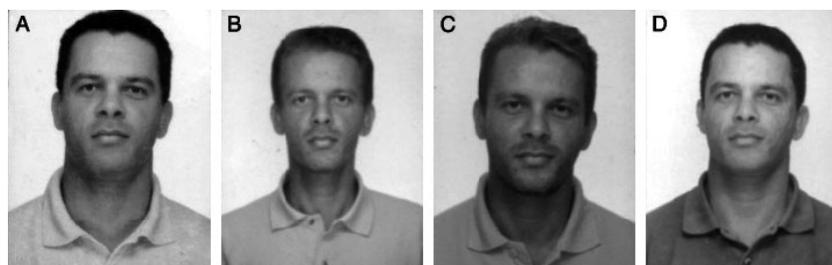


Fig. 1. Photographs of the face of a patient (of the group A), with an esophageal ulcer of 6 cm, who used the dietary supplementation with melatonin, vitamins and aminoacids, in four different time periods: (A) March 2002: before the ulcer appeared (patient weighed 80 kg); (B) October 12, 2003: during the period of the ulcer (patient weighed 40 kg); (C) November 14, 2003: after 32 days of treatment (patient weighed 70 kg); (D) July 2, 2004: after 9 months of treatment. The patient now has body weigh as of March 2002 (80 kg).

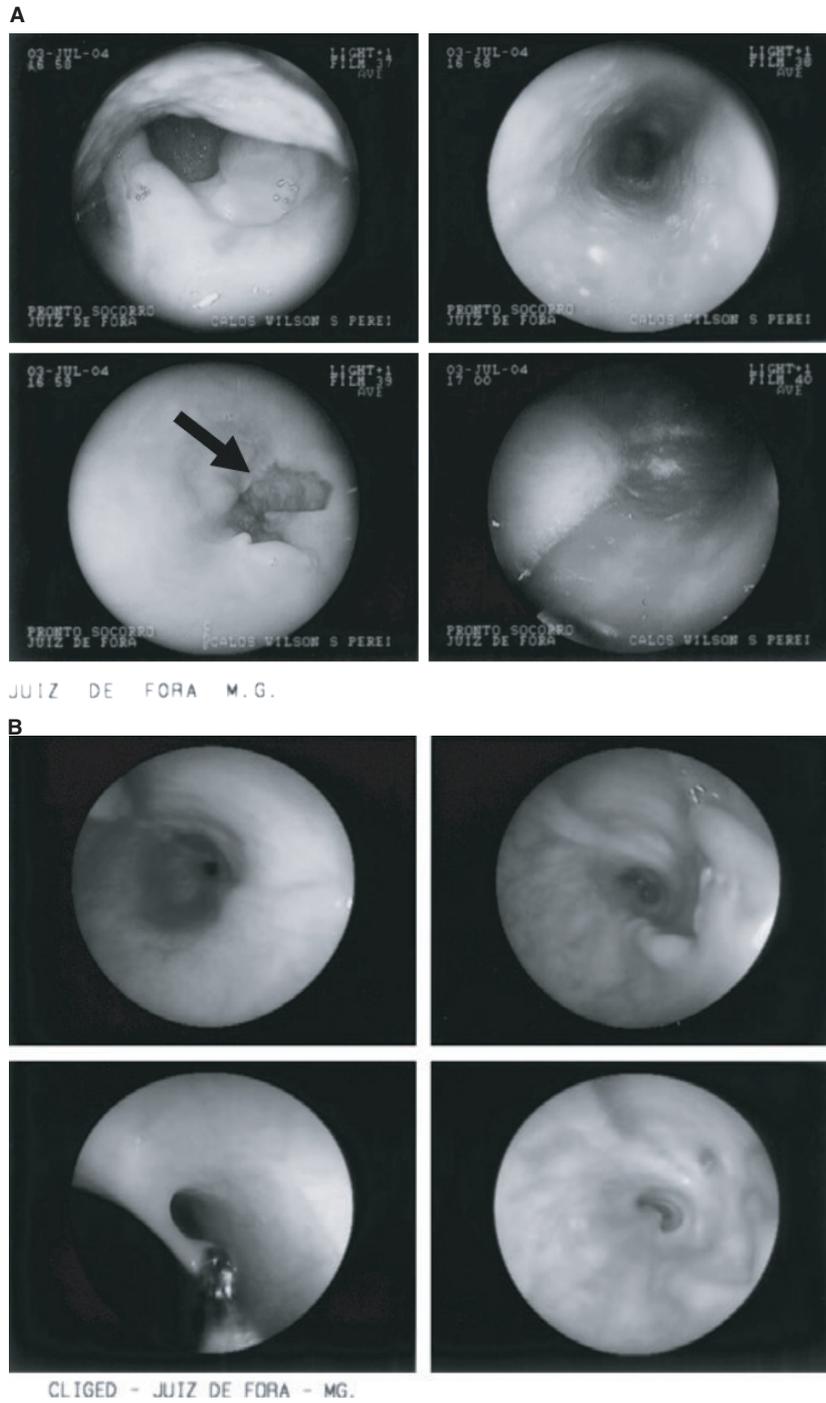


Fig. 2. Endoscopy records performed on patient (of the group A) in: (A) July 2003: showing the ulcer (indicated by an arrow); (B) July 2004: showing that the ulcer was practically disappeared after 9 months of treatment.

acids, and vitamins), and 65.7% (115/175) in group B (subjects who took omeprazole) ($P < 0.05$) (see Table 2).

Although one patient of group A (0.56%) has Fanconi Syndrome [a disorder in which the proximal renal tubules of the kidney do not properly reabsorb electrolytes and nutrients (aminoacids, vitamins, minerals, electrolytes, and bicarbonate), but instead ‘spill’ them in the urine] [24–26]; she was presumably healed of GERD because melatonin attenuates Fanconi Syndrome [27].

Patients of group B related more side effects than those of group A. Only somnolence was reported for supplementation of melatonin, vitamins and aminoacids during the treatment (see Table 3).

After the work complete, 60 subjects (34.3%) of group B, who reported persistence of the symptoms, used the supplement for 40 days. After this period, all patients (100%) of this subgroup reported that all symptoms disappeared.

Discussion

Probably, the regression of NERD/GERD symptoms and the relief of the pain was based on the following facts: the first biocompound of this formula is melatonin which has an inhibitory action on gastric acid secretion [20, 21], and effects on ulcer healing [21, 28–33] which involves hyperemia at ulcer margin [34, 35]. Ulcer healing and the gastroprotective effects of melatonin are specifically mediated by the interaction of this indole with melatonin MT2 receptors [21].

Transient lower esophageal sphincter relaxation (TLESR) is a major mechanism of reflux in patients with GERD. The sphincter is, therefore, an attractive target for pharmacotherapy [36]. Several agents have been shown to reduce the rate of TLESR including morphine, somatostatin, nitric oxide synthase inhibitors, among others [37]. Melatonin inhibits nitric oxide biosynthesis [21, 22], which may explain the regression of GERD symptoms.

Tryptophan, vitamins B6 and B12, in high doses, can alleviate acute pain [38]. This analgesic effect is attributed to an increased availability and/or effectiveness of noradrenaline and serotonin acting as inhibitory transmitters in the nociceptive system [38]. Another ingredient is folic acid, which protects against gastroenterological cancers [39]. Probably, these biochemicals and other components of the formulation (betaine and methionine) induced synthesis of *S*-adenosyl-L-methionine (SAME) [40–42], a methyl donor, which has anti-inflammatory as well as analgesic activity without damaging the gastrointestinal mucosa of experimental animals [43]. Beyond that, SAME has been used to treat gastric ulcer in animals [44]. Economically, these biomolecules are less expensive than SAME and the capsules could be accessible to poorer populations.

A total of 159 patients (90.3%) of group A related somnolence and sleep improvement. This fact is explainable due to sleep-inducing activity of melatonin [45, 46]. So, this formulation can also be used by patients with sleep disorders.

Similar formulations using vitamins and aminoacids were tested, successfully, in nearly 10,000 patients with depression [47–49], proving that there are no significant side effects in this formulation.

Fig. 1 shows photographs of the face of a patient (of the group A) who used the supplementation with melatonin, vitamins and aminoacids, in four different time periods. After 32 days of treatment, he had recovered 30 kg. In photos taken in October and November of 2003, the color of his hair was yellow (Fig. 1B,C). The patient reported that his hair had changed color from black to yellow after the ulcer appeared (he did not dye his hair). This is consistent with the observations in rats where malnutrition changed hair color to yellow [50]. After treatment, the patient recovered the natural color of hair (Fig. 1D). Fig. 2 shows endoscopy records of the patient cited above performed before (Fig. 2A) and after (Fig. 2B) treatment.

The results obtained show that a therapy using a dietary supplement with melatonin, vitamins and aminoacids promotes regression of NERD/GERD symptoms. The results shown in this paper are highly significant, because the patients, who used the supplementation reported fewer

side effects than patients who used omeprazole. These results suggest that GERD is inhibited by low levels of melatonin and certain vitamins and aminoacids in the human. This formulation can also be used for treatment of sleep disorders, since 159 subjects (90.3%) of group A related sleep improvement.

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