CASE REPORT

# MELATONIN FOR THE TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE

Melvyn R. Werbach, MD

The enterochromaffin cells of the gastrointestinal (GI) tract secrete 400 times as much melatonin as the pineal gland; therefore, it is not surprising that research is finding that this indole plays an important role in GI functioning. In animal studies, it protects against GI ulcerations, and randomized clinical trials suggest its efficacy in treating functional dyspepsia and irritable bowel syndrome. Melatonin administration has been shown to protect against esophageal lesions in animals. Moreover, in a randomized, single-blind clinical trial of subjects with gastroesophageal reflux disease (GERD), the combination of melatonin with other natural supplements was found to be superior to omeprazole, a proton pump inhibitor (PPI). Its administration as a single treatment for GERD has not been previously reported.

A 64-year-old Caucasian female who required treatment with a PPI for symptoms of GERD wished to substitute a natural treatment because of the risk of worsening her osteoporosis. She experienced a return of symptoms following each of three 20-day trials of a proprietary blend of D-limonene when attempts were made to discontinue the PPI. She then underwent a trial of a natural formula consisting of melatonin 6 mg, 5-hydroxytryptophan 100 mg, D,L-methionine 500 mg, betaine 100 mg, L-taurine 50 mg, riboflavin 1.7 mg, vitamin $B_6$ 0.8 mg, folic acid 400 µg, and calcium 50 mg. After 40 days, the PPI was withdrawn without a return of symptoms. Subsequently, an attempt to reduce melatonin to 3 mg resulted in symptoms, while all other ingredients were withdrawn with minimal symptoms during 10 months of follow-up. (*Altern Ther Health Med.* 2008;14(4):54-58.)

**Melvyn R. Werbach, MD, is an associate editor of *Alternative Therapies in Health and Medicine.* He is also the author of several books on natural medicines, including *Nutritional Influences on Illness* (Keats Publishing, 1990) and *Textbook of Nutritional Medicine* (Third Line Press, 1999).**

Gastroesophageal reflux disease (GERD) can be defined as symptoms of mucosal damage produced by the abnormal reflux of gastric contents into the esophagus.[1] It is one of the most common diseases in the Western world.[2] For adults in the United States, symptoms of esophageal reflux are reported to occur in 44% of the population once a month,[3] in 20% once a week,[4] and in about 10% daily.[2]

Medical treatment has focused on combating stomach acid, the primary cause of inflammation of the esophageal mucosa. Proton pump inhibitors (PPIs) are currently the most potent acid suppressants and are a major source of income for the pharmaceutical industry. In the United States only the lipid regulating drugs have greater sales.[5]

Despite the popularity of PPIs, there are a growing number of concerns about their safety. Their long-term safety is not completely known, as studies investigating their long-term use have followed up their subjects for no more than 10 years.[6] In addition to common side effects (such as headaches, nausea, and diarrhea) that cease as soon as medication is stopped, they may be associated with a number of longer lasting adverse effects, which may be due to their profound acid suppression and the elevated level of gastrin that results from it. These include a significant increase in risk for hip fracture. For example, a large case-control study found a 44% increase in hip fracture risk in patients over age 50 who had received PPIs for more than 1 year. For those who received high doses, the risk increased 2.6 times.[7]

Another case-control study found that patients receiving PPIs had a 50% increase in risk for community-acquired pneumonia. In contrast to the increasing risk for hip fracture with continued intake of PPIs, patients who started ingesting PPIs within the past week had the greatest elevation in risk (500%), and the risk decreased over time to 33%.[8] Similarly, the use of PPIs is associated with an increased risk of *Clostridium difficile*–associated diarrhea among hospital patients.[9] PPIs are also the most common cause of drug-related acute interstitial nephritis,[10] and there is compelling evidence that PPIs may cause myopathies.[11]

Hypergastrinemia causes rebound hyperacidity when the drug is stopped, and animal studies suggest that it may eventually cause enterochromaffin-like cell hyperplasia and carcinoids,[12] whereas drug-induced gastric hypoacidity increases gut bacterial infections and may possibly increase the risk of viral and prion infections.[13]

Finally, gastric acid is needed for the proper absorption of several important nutrients, and thus potent acid suppression

may provoke deficiencies. Vitamins whose absorption is acid-dependent include vitamin $B_{12}$[14] and vitamin C.[15] Acid-dependent minerals include calcium, iron, magnesium, phosphorus, and zinc.[6]

There is thus a need for a safer approach to treating GERD. This article presents the first report of melatonin administration as a treatment for the symptoms of GERD and reviews the evidence for the efficacy of the indole in this disorder.

Melatonin is widely recognized as a pineal hormone. Most healthcare professionals are unaware, however, that this indole is secreted not only in the pineal gland but also in the gut. In fact, the quantity of melatonin secreted by the enterochromaffin cells in the gastrointestinal (GI) tract is 400 times that of the pineal.[16] In contrast to pineal melatonin, the release of GI melatonin appears to be related to the periodicity of food intake.[16]

Compared to pharmaceuticals, melatonin is tolerated extremely well.[17] One study found no harmful side effects at doses as high as 60 mg daily.[18] In a safety analysis that included 487 participants in 10 studies, 9 of which were randomized controlled trials, the occurrences of the most commonly reported adverse events (headache, dizziness, nausea, and drowsiness) did not differ significantly from those associated with placebo.[19]

Due to its immunostimulating effects,[20] however, melatonin should be avoided by people with autoimmune disorders and, due to its possible effects on female hormones, it is not recommended for pregnant or nursing mothers. Moreover, although it has been found to be relatively safe over the short term (days to weeks), its safety over the long term has not been established.[21]

Melatonin has been shown to protect against GI ulcerations by several actions. It is a potent antioxidant,[22] it inhibits the secretion of hydrochloric acid and pepsin,[23] and it stimulates the immune system.[16] These actions increase microcirculation and promote regeneration of the luminal epithelium.[16]

Randomized clinical trials have found melatonin to be effective in treating functional dyspepsia, a disorder of the upper GI tract. Functional dyspepsia was studied in 60 patients aged 19 to 39 years without *Helicobacter pylori*.[24] The patients randomly received either melatonin 5 mg in the evening or placebo. Both groups were on an equivalent diet and were only to take an alkaline drug in case of abdominal pain. After 12 weeks, the dyspeptic symptoms completely subsided in 17 patients (56.6%) in the melatonin group, and another 9 patients (30%) showed a partial improvement. This contrasted with the placebo group, in which 93.3% failed to improve. Multivariate analysis indicated that melatonin correlated independently with significantly improved patient health. Past infection with *H pylori* decreased the positive effect of melatonin.[24]

Two studies also found melatonin to be effective in treating a lower GI disorder, namely irritable bowel syndrome (IBS). Findings from both suggest that the indole's efficacy was not due to improvements in sleep, anxiety, or depression. In the first study, 17 female patients randomly received either 3 mg of melatonin each evening or placebo for 8 weeks, followed by a 4-week washout period, and then melatonin or placebo in reverse order for another 8 weeks. Improvements in mean GI symptom scores (but not anxiety/depression or sleep scores) were significantly greater after treatment with melatonin than after placebo (3.9 vs 1.3; $P$=.037). The percentage of patients achieving a mild-to-excellent improvement was also greater after the melatonin-treatment arm (88% vs 47%; $P$=.04).[25]

In the second study of IBS patients, this time of patients with sleep disturbances, 40 patients (24 female) aged 20 to 64 years randomly received either 3 mg of melatonin or placebo at bedtime for 2 weeks. Compared with placebo, melatonin significantly decreased mean abdominal pain score (2.35 vs 0.70; $P$<.001) and increased mean rectal pain threshold (8.9 vs -1.2 mm Hg; $P$<.01). Bloating, stool type, stool frequency, and anxiety and depression scores were similar after treatment in both groups. Moreover, sleep parameters were unchanged.[26]

Evidence that melatonin specifically protects against esophageal damage comes from a study of acute esophageal injury in rats in which the esophagus was perfused with an acid-pepsin-bile solution. Pretreatment with melatonin was found to prevent esophageal injury in a dose-dependent manner.[27] Compared to healthy subjects, subjects with GERD found to have esophageal lesions also have diminished nocturnal melatonin secretion, although subjects with symptoms of GERD but normal esophageal findings have elevated nocturnal melatonin secretion.[28] This suggests that in populations prone to esophageal reflux disease, reduced melatonin secretion may fail to protect the esophageal mucosa from ulceration due to the adverse effects of acid-pepsin and bile salts.

Although no previous human study has provided melatonin as a single therapeutic agent to subjects with GERD, it was included as part of a nutritional formula in a randomized, single-blind, experimental study.[29]

Patients with heartburn, regurgitation, dysphagia, and chest pain were enrolled in the study if they experienced at least 1 period of moderate-to-very-severe heartburn or regurgitation in the 7 days prior to the experimental treatment. In addition to 6 mg of melatonin, the formula contained several other nutrients. These ingredients, their dosages, and the author's rationales for them are as follows:

> *L-tryptophan (200 mg), vitamin $B_6$ (25 mg), and vitamin $B_{12}$ (50 mcg) may alleviate acute pain due to enhanced availability and/or efficacy of the neuroinhibitors noradrenaline and serotonin. Folic acid 10 mg protects against GI cancers. These substances, in combination with betaine (100 mg) and methionine (100 mg), probably induced synthesis of S-adenosyL-L-methionine (SAMe), a methyl donor with anti-inflammatory and analgesic activity, which has successfully treated gastric ulcer in animals.*[30]

A total of 351 patients entered the study. After randomization, 176 patients received the formula (group A), and 175 patients received 20 mg omeprazole (group B), each taken after

the evening meal for 40 days. Before the study 18.2% of patients in group A vs 10.8% of patients in group B had received medication for reflux disease. No other medication was allowed for the duration of the study.

Seven days after starting the formula, all subjects in group A reported symptom relief, and by the end of the study (following 40 days of treatment), all subjects in group A rated themselves as markedly improved (ie, asymptomatic). Of the 176 subjects, 159 (90%) noted what they described as either somnolence or sleep improvement.

In group B, 115 subjects (65.7%) reported symptom relief 9 days after starting omeprazole treatment, and 2.3% reported partial relief (ie, slight improvement); the remainder reported no change. Two subjects in the group (1.1%) withdrew from the study because of persistent headache. Moreover, 7 subjects (4%) noted diarrhea, 4 subjects (2.3%) noted somnolence or sleep improvement, and 3 subjects (1.7%) noted hypertension.

Following completion of the randomized study, the 60 subjects (34.3%) in group B who reported persistence of their symptoms received the formula for 40 days. All subjects in this subgroup reported disappearance of all GERD symptoms by the end of the 40-day period.[29]

Although he was impressed by the results of this study, the author was suspicious that melatonin was the key ingredient of the formula. Through the means of an unblinded case study, he conducted a preliminary investigation of the efficacy of melatonin alone as a treatment for GERD.

**CASE REPORT**

The patient was a 64-year-old Caucasian female who, after fasting since the previous night's dinner, experienced a sudden episode of severe pain in her chest and up into her mouth around 1 PM. She ate food and the pain largely dissipated, although slight discomfort remained.

She received a medical evaluation 2 days later and was started on 40 mg daily of pantoprazole, a PPI, with full symptom relief. Two weeks later, however, mild pain returned in the same areas despite continuation of the medication. She took calcium carbonate 1000 mg, and the symptoms stopped.

Concerned that pantoprazole might not fully control symptoms and that long-term use of a PPI could worsen her osteoporosis, her physician decided to attempt to substitute a natural treatment. The plan was to first add the natural treatment for a period of time and then to attempt to discontinue medication in the hope that symptoms would not return.

D-limonene was selected for the initial trial and was provided in the form of a proprietary extract of orange peel (*Citrus sinensis*) that was standardized to contain a minimum of 98.5% of D-limonene. This selection was made because although there are no published studies, the manufacturer has reported excellent results in its proprietary study. Specifically, 89% of 19 subjects in the manufacturer's study reported resolution of most of their gastric distress after taking one 1000-mg gelcap of standardized D-limonene every other day.

In the controlled, double-blind, second phase of the study, 22 subjects randomly received either the standardized extract or placebo. Seventy-five percent of subjects receiving standardized D-limonene reported significant relief after 2 weeks compared to 20% of those receiving placebo. No adverse effects were reported, and some participants reported relief lasting up to 6 months (Willette RC, Barrow L, Doster R, Wilkins J, Wilkins JS, Heggers JP, unpublished data).

The patient was placed on the manufacturer's recommended 20-day course of 1000 mg of D-limonene every other day and stopped pantoprazole following the conclusion of the course of D-limonene. Ten days later sharp pain suddenly started under her right breast at 6 PM. She immediately took famotidine 10 mg (a histamine H2-receptor antagonist) and calcium carbonate 1000 mg, with relief after 15 minutes. She was then switched to esomeprazole, a PPI, 20 mg daily, and remained asymptomatic.

After being asymptomatic for 12 days, esophagoscopy showed evidence of a hiatal hernia with minimal gastritis and a normal duodenum. Gastric biopsies were normal and negative for *H pylori*. She was told to continue on esomeprazole 20 mg daily. After 1 month, she stopped esomeprazole on her own without a return of symptoms.

Two and a half months later, in order to improve her lipid profile, she was started on 20 mg daily of lovastatin (an HMG-CoA reductase enzyme inhibitor which may cause upper GI symptoms such as nausea, "gas pains," and chest pain). She developed "gas pains" 5 days later and took calcium carbonate 1000 mg. Although she had full symptom relief, the next day she noted moderate pain under her right breast that continued until she returned to esomeprazole 20 mg daily.

Two further trials of substituting D-limonene for the medication also were unsuccessful. She was then switched to 20 mg daily of omeprazole, another PPI, and continued to be totally asymptomatic.

Eighteen months later, however, she sought a trial of another natural treatment. This time she was placed on a combination of dietary supplements modeled after the formula described earlier in this article.[29] Ingredients consisted of 5-hydroxytryptophan (5-HTP) 100 mg, a proprietary methionine complex (consisting of D,L-methionine 500 mg, betaine 100 mg, L-taurine 50 mg, riboflavin 1.7 mg, vitamin $B_6$ 0.8 mg, folic acid 400 µg, and calcium 50 mg) 1 capsule, and melatonin 6 mg, all to be taken at bedtime. (See the Table for a side-by-side comparison of the 2 formulas.) Forty days later, she stopped omeprazole without the return of symptoms.

It was decided after 1 month that the combination formula appeared to be effective, and a series of trials were begun to attempt to minimize the ingredients of her anti-GERD supplement. Initially, an attempt was made to reduce the melatonin dosage to half (3 mg) by doubling the dosage of 5-HTP (a melatonin precursor) to 200 mg. She developed nausea for 30 minutes, however, around the middle of the next 2 mornings while still fasting. Omeprazole 20 mg daily was restarted along with the anti-GERD formula.

Comparison of Anti-GERD Experimental Formulas

| de Souza Pereira anti-GERD Formula | Modified anti-GERD Formula |
|---|---|
| Melatonin 6 mg | Melatonin 6 mg |
| L-tryptophan 200 mg | 5-hydroxytryptophan 100 mg |
| D,L-methionine 100 mg | Proprietary methionine complex: |
| Betaine 100 mg | D,L-methionine 500 mg |
| Folic acid 10 mg | Betaine 100 mg |
| Vitamin $B_6$ 25 mg | Folic acid 400 µg |
| Vitamin $B_{12}$ 50 µg | Vitamin $B_6$ 0.8 mg |
| | Riboflavin 1.7 mg |
| | Calcium 50 mg |
| | L-taurine 50 mg |

A second attempt to reduce the melatonin dosage was made 2 weeks later. Omeprazole was discontinued, and melatonin was reduced again to 3 mg daily, but this time the 5-HTP dosage was tripled to 300 mg. Around midday the following day, she suddenly experienced sharp pain between her breasts and in her mouth and tongue. Omeprazole 20 mg daily was immediately restarted, with full symptom relief, and she returned once again to the initial anti-GERD formula. One month later, she stopped omeprazole without the return of symptoms.

Next, attempts were made to discontinue the other ingredients of the anti-GERD formula while continuing melatonin at the same dosage. First the methionine complex was stopped successfully, and then the 5-HTP was stopped successfully, so that her treatment now consisted solely of melatonin.

Two months later she was on a trip and awoke at 5 AM with sharp pain between her breasts (7 on a 1-10 scale) that lessened upon standing. She counted the number of melatonin tablets she had brought with her and discovered that she had forgotten to take the supplement the night before. For 1 week she returned to omeprazole 20 mg daily in addition to melatonin 6 mg at bedtime.

Over the next 6 months of follow-up, she has continued on melatonin 6 mg at bedtime. Except for 3 episodes of mild substernal chest pain awakening her during the middle of the night, she has remained asymptomatic. (During each episode she took omeprazole 20 mg, experienced full pain relief in about 30 minutes, and then returned to sleep.)

## DISCUSSION

This appears to be the first published study to record the successful substitution of melatonin 6 mg at bedtime for the maximum recommended dosage of a PPI in a patient with GERD. The report suffers from 2 serious limitations. First, since it documents only a single case, it provides no indication of whether the findings can be generalized to other patients. Second, it fails to control for the placebo effect, so it is not possible to know whether the active treatment or a concurrent nonspecific factor is responsible for her response.

Perhaps the strongest indication that her response was unlikely to be due to the placebo effect was her discovery after the symptoms started that she had skipped taking melatonin the night before; thus her symptoms occurred even though she thought she was being protected by the pill. Further evidence suggesting that her response was not simply a placebo effect was her poor prior response to multiple trials of D-limonene, another natural agent that had been presented to the patient in a similar manner.

Asymptomatic on the combination supplement without the PPI, she was successfully weaned off of all of its ingredients except for melatonin, for which a 50% decrease in dosage led to the rapid return of symptoms. We cannot conclude, however, that the other ingredients were ineffective as it is possible that they had an initial role in repairing mucosal defenses so that melatonin alone would become adequate for treatment.

It appears that, through various mechanisms, melatonin protects the esophageal mucosa from injury due to the assault of acid reflux. Daily administration appears to be necessary, or symptoms immediately recur.

Despite its efficacy in preventing symptoms for almost a year, it is possible that symptoms may recur at a later date, perhaps due to worsening of the underlying disorder.

This report also addressed the question of whether 5-HTP, a melatonin precursor, could be substituted for melatonin in relieving the symptoms of GERD. The oral administration of L-tryptophan, the immediate precursor to 5-HTP, to chicks and rats has been found to cause a rapid, dose-dependent elevation of circulating melatonin, and the major source of the increase in circulating melatonin was not the pineal gland but the enterochromaffin cells of the GI tract.[31] Other studies suggest that this increase may be roughly 4-fold compared to baseline levels.[32,33]

In the case presented here, an attempt was made to reduce the initial melatonin dosage by doubling and then by tripling the dosage of 5-HTP. However, 300 mg of 5-HTP, a dosage usually considered to be adequate for clinical applications, failed to permit melatonin to be reduced from 6 mg to 3 mg daily, and discontinuation of 5-HTP alone did not cause a return of symptoms. These findings suggest that the usual clinical dosages of 5-HTP are ineffective as a substitute for melatonin.

## CONCLUSIONS

Findings of this single case study in addition to a review of the literature suggest that melatonin 6 mg at bedtime may be an effective treatment for GERD with fewer and less serious adverse effects than acid-reducing medications so long as anti-GERD medications are (1) continued during the first 40 days of treatment and (2) resumed for at least 1 dose whenever symptoms recur. Further studies, including randomized controlled trials, are needed to validate and extend these early findings.

### REFERENCES


1. DeVault KR, Castell DO; American College of Gastroenterology. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. *Am J Gastroenterol*. 2005;100(1):190-200.
2. Orlando RC. Diseases of the esophagus. In: Goldman L, Ausiello D, eds. *Cecil Textbook of Medicine*, 22nd ed. Philadelphia, PA: Saunders, 2004.

3. Locke GR 3rd, Talley NJ, Fett SL, Zinsmeister AR, Melton LJ 3rd. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmstead County, Minnesota. *Gastroenterology*. 1997;112(5):1448-1456.
4. The Gallup Organization. *A Gallup Survey on Heartburn Across America*. Princeton, NJ, 1988.
5. *IMS National Sales Perspectives. 2007 Top Therapeutic Classes by US Sales*. Available at: http://imshealth.com/vgn/images/portal/CIT_40000873/39/60/834330392007%20Top%20Therapeutic%20Classes%20by%20Sales.pdf. Accessed May14, 2008.
6. Malaty W, Stigleman S, Mayer J, Guthmann RA. Clinical inquiries. Is the long-term use of proton pump inhibitors safe? *J Fam Pract*. 2004;53(9):740-742.
7. Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA*. 2006;296(24):2947-2953.
8. Gulmez SE, Holm A, Frederiksen H, Jensen TG, Pedersen C, Hallas J. Use of proton pump inhibitors and the risk of community-acquired pneumonia: a population-based case-control study. *Arch Intern Med*. 2007;167(9):950-955.
9. Yearsley KA, Gilby LJ, Ramadas AV, Kubiak EM, Fone DL, Allison MC. Proton pump inhibitor therapy is a risk factor for Clositridium difficile-associated diarrhea. *Aliment Pharmacol Ther*. 2006:24(4):613-619.
10. Brewster UC, Perazella MA. Proton pump inhibitors and the kidney: critical review. *Clin Nephrol*. 2007:68(2):65-72.
11. Clark DW, Strandell J. Myopathy including polymyositis: a likely class adverse effect of proton pump inhibitors? *Eur J Clin Pharmacol*. 2006:62(6):473-479.
12. Nørsett KG, Lægreid A, Langaas M, et al. Molecular characterization of rat gastric mucosal response to potent acid inhibition. *Physiol Genomics*. 2005;22(1):24-32.
13. Waldum HL, Brenna E, Sandvik AK. Long-term safety of proton pump inhibitors: risks of gastric neoplasia and infections. *Expert Opin Drug Saf*. 2002;1(1):29-38.
14. Valuck RJ, Ruscin JM. A case control study on adverse effects: H2 blocker or proton pump inhibitor and risk of vitamin $B_{12}$ deficiency in older adults. *J Clin Epidemiol*. 2004;57(4):422-428.
15. Henry EB, Carswell A, Wirz A, Fyffe V, McColl KE. Proton pump inhibitors reduce the bioavailability of dietary vitamin C. *Aliment Pharmacol Ther*. 2005;22(6):539-545.
16. Bubenik GA. Gastrointestinal melatonin: localization, function, and clinical relevance. *Dig Dis Sci*. 2002;47(10): 2336-2348.
17. Hardeland R, Randi-Perumal SR. Melatonin, a potent agent in antioxidative defense: actions as a natural food constituent, gastrointestinal factor, drug and prodrug. *Nutrition Metab (Lond)*. 2005 Sep 10;2:22.
18. Jacob S, Poeggeler B, Weishaupt JH, et al. Melatonin as a candidate compound for neuroprotection in amyotrophic lateral sclerosis (ALS): high tolerability of daily oral melatonin administration in ALS patients. *J Pineal Res*. 2002;33(3):186-187.
19. Buscemi N, Vandermeer B, Hooton N, et al. Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: meta-analysis. *BMJ*. 2006;332(7538):385393.
20. Carrillo-Vico A, Guerrero JM, Lardone PJ, Reiter RJ. A review of the multiple actions of melatonin on the immune system. *Endocrine*. 2005;27(2):189-200.
21. Buscemi N, Vandermeer B, Pandya R, et al. *Melatonin for Treatment of Sleep Disorders*. AHRQ Publication No. 05-E002-2. Rockville, MD: Agency for Healthcare Research and Quality, US Department of Health and Human Services; 2004.
22. Reiter RJ, Tan DX, Mayo JC, Saintz RM, Leon J, Czarnocki Z. Melatonin as an antioxidant: biochemical mechanisms and pathophysiological implications in humans. *Acta Bioch Pol*. 2003;50(4):1129-1146.
23. Kato K, Murai J, Asai S, et al. Central nervous system action of melatonin on gastric acid and pepsin secretion in pylorus-ligated rats. *Neuroreport*. 1998;9(17):3989-3992.
24. Klupinska G, Poplawski T, Drzewoski J, et al. Therapeutic effect of melatonin in patients with functional dyspepsia. *J Clin Gastroenterol*. 2007;41(3):270-274.
25. Lu WZ, Gwee KA, Moochhalla S, Ho KY. Melatonin improves bowel symptoms in female patients with irritable bowel syndrome: a double-blind placebo-controlled study. *Aliment Pharmacol Ther*. 2005;22(10):927934.
26. Song GH, Leng PH, Gwee KA, Moochlala SM, Ho KY. Melatonin improves abdominal pain in irritable bowel syndrome patients who have sleep disturbances: a randomised, double blind, placebo controlled study. *Gut*. 2005;54(10):1402-1407.
27. Konturek SJ, Zayachkivska O, Havryluk XO, et al. Protective influence of melatonin against acute esophageal lesions involves prostaglandins, nitric oxide and sensory nerves. *J Physiol Pharmacol*. 2007;58(2):361-377.
28. Klupinska G, Wisniewska-Jarosinska M, Harasiuk A, et al. Nocturnal secretion of melatonin in patients with upper digestive tract disorders. *J Physiol Pharmacol*. 2006;57 Suppl 5:41-50.
29. de Souza Pereira R. Regression of gastroesophageal reflux disease symptoms using dietary supplementation with melatonin, vitamins and aminoacids: comparison with omeprazole. *J Pineal Res*. 2006;41(3):195-200.
30. GERD, melatonin, vitamins and amino acids: Kirk Hamilton interviews Ricardo de Souza Pereira [transcript]. *The Experts Speak*. Available at: http://www.vitasearch.com/CP/experts/RDSPereiraAT10-30-06.htm. Accessed May 14, 2008.
31. Huether G, Poeggeler B, Reimer A, George A. Effect of tryptophan administration on circulating melatonin levels in chicks and rats: evidence for stimulation of melatonin synthesis and release in the gastrointestinal tract. *Life Sci*. 1992;51(12):945-953.
32. Yaga K, Reiter RJ, Richardson MA. Tryptophan loading increases daytime serum melatonin levels in intact and pinealectomized rats. *Life Sci*. 1993;52(14):1231-1238.
33. Brzozowski T, Konturek PC, Konturek SJ, et al. The role of melatonin and L-tryptophan in prevention of acute gastric lesions induced by stress, ethanol, ischemia, and aspirin. *J Pineal Res*. 1997;23(2):79-89.