

Is it necessary to increase the dose of levothyroxine in patients with hypothyroidism who use omeprazole?

É necessário aumentar a dose de levotiroxina em pacientes com hipotireoidismo que usam omeprazol?

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ABSTRACT

Objective: It is believed that gastric pH interferes in levothyroxine absorption. Omeprazole, which acts by blocking the secretion of gastric acid, might interfere in hypothyroidism control in patients using levothyroxine and this effect could be dose dependent. The present study aimed to investigate this possibility. **Subjects and methods:** Twenty-one patients with primary hypothyroidism who had been using a stabilized levothyroxine dosage for at least one year were selected and randomly assigned to take omeprazole at the dosage of 40 mg or 20 mg per day. The mean levels of thyroid-stimulating hormone (TSH) before and 3 months after omeprazole usage were compared in the entire sample and in each group. **Results:** Ten patients concluded the entire treatment protocol in the 20 mg group and nine patients in the 40 mg group. There was no significant difference in TSH levels before and 3 months after omeprazole treatment in the entire patient sample (median levels: 2.28 vs. 2.30 mU/L, respectively; $p = 0.56$). Analysis of each subgroup (20 and 40 mg) showed no significant variation in TSH levels before and 3 months after omeprazole treatment (median levels: 2.24 vs. 2.42 mU/L, $p = 0.62$, and 2.28 vs. 2.30 mU/L, $p = 0.82$, respectively). No significant difference in the absolute ($p = 0.93$) or relative ($p = 0.87$) delta were observed between the two subgroups. **Conclusion:** Omeprazole in the dosage of 20 or 40 mg/day does not interfere in a clinically relevant manner in the treatment of patients with hypothyroidism that was previously under control. *Arq Bras Endocrinol Metab.* 2014;58(7):731-6

Keywords

Hypothyroidism; thyroxine; absorption; omeprazole; proton pump inhibitors

RESUMO

Objetivo: Acredita-se que o pH gástrico possa interferir na absorção de levotiroxina. O omeprazol, ao inibir a secreção de ácido gástrico, poderia interferir no controle do hipotireoidismo em pacientes em uso de levotiroxina de forma dose-dependente. O presente estudo tem como objetivo investigar essa hipótese. **Sujeitos e métodos:** Vinte e um pacientes em uso de dose estável de levotiroxina por no mínimo um ano foram incluídos e aleatoriamente selecionados para iniciar o uso de omeprazol na dose de 40 mg ou 20 mg por dia. Foram comparados os níveis médios de hormônio tireoestimulante (TSH) antes e 3 meses após o uso de omeprazol, na amostra total e em cada grupo. **Resultados:** Dez pacientes concluíram o protocolo de tratamento no grupo de 20 mg e nove, no grupo de 40 mg. Não houve diferença significativa nos níveis de TSH antes e 3 meses após terapia com omeprazol na amostra total de pacientes (média: 2,28 vs. 2,30 mU/L, respectivamente; $p = 0,56$). A análise de cada subgrupo (20 e 40 mg) não demonstrou variação significativa nos níveis de TSH antes e 3 meses após terapia com omeprazol (média: 2,24 vs. 2,42 mU/L, $p = 0,62$ e 2,28 vs. 2,30 um/L, $p = 0,82$, respectivamente). Não houve diferença significativa no delta absoluto ($p = 0,93$) ou relativo ($p = 0,87$) entre os dois subgrupos. **Conclusão:** Omeprazol na dose de 20 ou 40 mg/dia não interfere de forma clinicamente relevante no tratamento de pacientes com hipotireoidismo previamente bem controlados. *Arq Bras Endocrinol Metab.* 2014;58(7):731-6

Descritores

Hipotireoidismo; tiroxina; absorção; omeprazol; inibidores da bomba de prótons

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INTRODUCTION

The treatment of hypothyroidism, which is based on the oral reposition of levothyroxine (L-T4), is simple and safe. However, the erratic absorption and narrow therapeutic window of L-T4 make treatment susceptible to interference from various confounding factors. Physiologic conditions such as pregnancy and aging, diseases that modify hormone absorption or its metabolism, as well as various medications, affect the L-T4 dose needed for the adequate treatment of hypothyroidism (1).

The reduction in absorption of L-T4 by antacid medications (aluminum hydroxide) (2) and recent studies associating diseases characterized by hypochloridria (3,4) with higher needs of the hormone have led to the hypothesis that gastric acidity plays a major role in L-T4 absorption. Proton-pump-inhibitors, which act by blocking the secretion of gastric acid through covalent bonds to the H⁺/K⁺ ATPase enzyme, are widely used for the treatment of common diseases, such as dyspepsia, gastroesophageal reflux, peptic ulcer, and acute gastric lesion prophylaxis in critical patients. In clinical practice, the administration of omeprazole to patients with hypothyroidism is common. Some studies were designed to evaluate the interaction of proton-pump-inhibitors and L-T4, but the results to date have been controversial (3,5-7). Therefore, due to the scarcity and controversy of the data published so far, the present study aimed to objectively evaluate if there is any interference in the treatment of hypothyroidism by omeprazole usage and whether this interaction, if proven to be real, would be dose dependent. In addition, if TSH levels outside of normal ranges were observed, then a secondary objective of the study was to characterize and quantify changes in L-T4 requirements during the period of omeprazole intake.

PATIENTS AND METHODS

Study design and patient selection

Patients receiving outpatient follow-up care at Clementino Fraga Filho University Hospital between May 2009 and April 2010 were selected for this study. The study was approved by the Ethical Committee of Clementino Fraga Filho University Hospital.

Inclusion criteria were as follows: 1) patients between 18 and 70 years of age; 2) a diagnosis of primary hypothyroidism with persistently normal levels of

TSH for at least one year in patients using stable doses of L-T4; 3) patients treated with same brand of L-T4 (Puran T4[®]); and 4) a clinical indication for omeprazole usage, such as dyspepsia, gastroesophageal reflux or peptic ulcer. Exclusion criteria included the following: 1) diseases or conditions associated with malabsorption, including celiac disease, intestinal inflammatory disease, short gut syndrome, atrophic gastritis, colestastic disease, hepatic cirrhosis, or history of gastric resection or bypass involving the small intestine; 2) usage of one of the following medications in the last six months: phenobarbital, phenytoin, carbamazepine, rifampin, amiodarone, sucralfate, iron sulfate, aluminum hydroxide, hormone reposition, H₂-antagonists or calcium carbonate; 3) pituitary disease; 4) pregnancy; or 5) usage of proton-pump inhibitors in the previous year.

Patients selected for the study were given omeprazole doses of 40 mg or 20 mg per day. They were advised to take L-T4 in fasting state, wait for 30 minutes before taking omeprazole and have breakfast only after 15 minutes. The first selected patient was assigned to the group using 20 mg. The subsequent patients were assigned alternately to each group consecutively, following the order of enrollment in the study. During the entire period of the study, the administration of drugs that might interfere in L-T4 action was avoided and participants were instructed not to use any medication without first consulting with the main researcher of the study.

All patients had TSH levels measured three months after the beginning of omeprazole therapy. In case of TSH variation to values above or below the normal range, L-T4 dosages were readjusted and the follow-up for omeprazole use was extended for two more months, at which time the TSH levels were re-assessed. Patients were reevaluated on at least two different occasions: before starting omeprazole therapy and within three months of starting the therapy. Treatment adherence was evaluated through pill counting. Satisfactory compliance was defined as more than 90% of pills taken as prescribed. During the study period, patients were given omeprazole (Neoprazol[®]) and L-T4 (Puran T4[®]) for free.

TSH assay

Serum TSH levels were measured by third generation chemiluminescence assay, and a concentration of 0.35-5.5 mU per liter was considered a normal range. For this assay, the Advia Centaur[®] kit (Siemens Medical Care, Tarrytown, NY) was used, which has a sensi-

vity of 0.008 mU/L, intraassay variation coefficient of 1.95-4.69%, and interassay variation coefficient of 3.62-4.28%.

Statistical analysis

We calculated that the total sample size required to provide 80% power to detect a TSH variation above 0,9 mUI/L before and after 3 months of omeprazole intake, at the 5% level of significance, was 19 patients. Assuming a drop-out rate of 10%, we estimated that we would need to enroll 21 patients.

A Mann-Whitney test was used to compare continuous variables between the groups, and categorical comparisons were performed using Fisher's exact test.

The Wilcoxon signed-rank test was used to verify whether any significant variation existed between basal TSH levels and the TSH levels measured after three months of treatment. The delta comparison between the groups was analyzed by the Mann-Whitney test.

Non-parametric tests were used, since TSH did not show a normal (Gaussian) distribution due to data dispersion, lack of distribution symmetry, and the small size of the sample. Log transformation of TSH values did not contribute in a relevant way to the analysis, and therefore it was discarded from the analysis. The adopted significance determination criterion was the 5% level. Statistical analysis was processed using SAS 6.11 software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Twelve patients were initially included in the 20 mg dose group, of which ten concluded their participation in the study. Two patients were excluded: one due to treatment withdrawal and another due to suspicion of omeprazole allergy that occurred immediately after the start of therapy, leading to treatment interruption. Serum TSH levels from both patients remained normal after their period of omeprazole therapy. In the 40 mg group, 9 patients were included and all of them concluded their participation in the study. Treatment compliance was considered satisfactory in both groups (more than 90% of pills taken as prescribed).

The group of patients using omeprazole 20 mg was composed of 8 women and 2 men, with a mean age of 54.6 ± 10.9 years, whereas the 40 mg group was composed of 8 women and 1 man, with a mean age of 50.6 ± 10.2 years. The groups were similar in age, sex and dosage of L-T4.

Whole sample analysis

No significant variation in TSH levels before drug administration and three months after omeprazole treatment was found when all patients were analyzed (median levels: 2.28 vs. 2.30 mU/L, respectively; $p = 0.56$) (Table 1 and Figure 1).

Table 1. Analysis of TSH levels at baseline and 3 months after omeprazole in the entire patient sample (19 patients)

TSH	Mean	SD/SE	Median	Minimum	Maximum	<i>P</i> value ^a
Baseline (mU/L)	2.48	1.12	2.28	0.42	5	
3 months after (mU/L)	2.76	1.75	2.30	0.28	5.69	
Absolute delta (mU/L)	0.28	0.36	0.06	-3.07	3.57	0.56
Relative delta (%)	29.8	24.1	1.2	-91.6	323.8	0.76

SD: standard deviation; SE: standard error: only for the deltas.

^a Wilcoxon-flagged posts test.

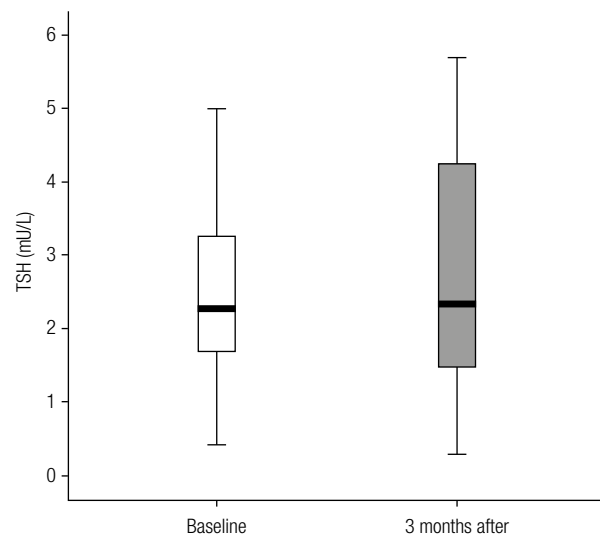


Figure 1. TSH levels before and 3 months after omeprazole treatment in the whole sample. Each box plot shows the median (horizontal line within the box) and the interquartile range (the horizontal lines at either end of the box). The ends of whiskers represent the minimum and maximum TSH levels.

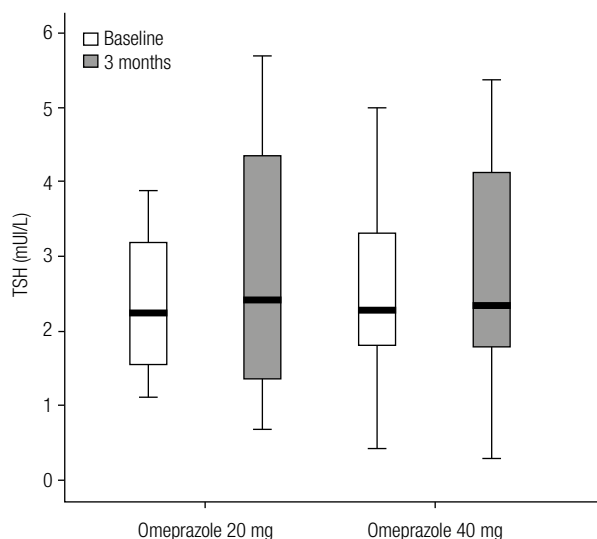
Patient group given omeprazole 20 mg per day

In the 20 mg group, no significant variation in the TSH before and after three months of treatment was observed (median levels: 2.24 vs. 2.42 mU/L, $p = 0.62$) (Table 2 and Figure 2).

Table 2. Analysis of TSH levels at baseline and 3 months after omeprazole in the 20 mg group

TSH	Mean	SD/SE	Median	Minimum	Maximum	p value ^a
Baseline (mU/L)	2.45	0.98	2.24	1.11	3.89	
3 months after	2.80	1.80	2.42	0.67	5.69	
Absolute delta (mU/L)	0.35	0.46	-0.15	-1.27	2.92	0.62
Relative delta (%)	15.7	25.0	-14.3	-53.7	204.2	0.92

SD: standard deviation; SE: standard error: only for the deltas.

^a Wilcoxon-flagged posts test.**Figure 2.** TSH levels before and 3 months after omeprazole treatment in each subgroup (20 mg and 40 mg). Each box plot shows the median (horizontal lines within the box) and the interquartile range (the horizontal lines at either end of the box). The ends of the whiskers represent the minimum and maximum TSH levels.

By the end of the three-month follow-up, TSH levels remained within the normal range in 9 of the 10 patients using omeprazole 20 mg per day. The TSH levels were above the upper limit (5.69 mU/L) of the normal range in only one patient. In this patient, the L-T4 dose was increased by 17% and omeprazole therapy was extended for two additional months. The TSH levels after this period returned to normal.

Patient group given omeprazole 40 mg per day

In the 40 mg group, no significant variation in the TSH levels before and after three months of treatment was observed (median levels: 2.28 *vs.* 2.30 mU/L, respectively; $p = 0.82$) (Table 3).

From the 9 patients using omeprazole 40 mg per day, 8 had TSH levels within the normal range after 3

Table 3. Analysis of TSH levels at baseline and 3 months after omeprazole in the 40 mg group

TSH	Mean	SD/SE	Median	Minimum	Maximum	p value ^a
Baseline (mU/L)	2.51	1.33	2.28	0.42	5	
3 months after (mU/L)	2.71	1.79	2.30	0.28	5.37	
Absolute delta (mU/L)	0.20	0.60	0.06	-3.07	3.57	0.82
Relative delta (%)	45.5	43.8	1.2	-91.6	323.8	0.65

SD: standard deviation; SE: standard error: only for the deltas.

^a Wilcoxon-flagged posts test.

months of treatment. TSH levels after that period was below the lower limit of the normal range in only one patient. In this patient, the L-T4 dose was decreased by 16% and proton-pump-inhibitor therapy was extended for two additional months. The TSH levels after this period returned to normal.

Comparison between the two groups

Basal TSH levels between the two groups did not reach a statistically significant difference (median levels: 2.24 *vs.* 2.28 mU/L, respectively; $p = 0.93$), and the levels in both groups evolved in a similar way with no significant difference in the absolute delta ($p = 0.93$) or relative delta ($p = 0.87$) of TSH levels between the two groups (Tables 2 and 3 and Figure 2).

DISCUSSION

In this pilot study, we found that in patients with hypothyroidism under control, omeprazole did not affect treatment with L-T4, regardless of the dosage used. The study aimed to evaluate whether omeprazole usage interfered with L-T4 action in patients with hypothyroidism, and if so, verify whether this interaction was dose dependent. This is the first clinical study to evaluate the interaction between omeprazole and L-T4 in patients with hypothyroidism.

To date, two other clinical studies have explored this interaction, and the results of those studies seem to have confirmed the interaction between proton-pump inhibitors and L-T4. Nevertheless, the previous studies differed from our study in certain aspects that may explain the apparent disparity.

Centanni and cols. studied a prospective cohort of patients with atoxic multinodular goiter in which the L-T4 dosage (Eutirox®) required for suppression of TSH levels was evaluated. In that study, 10 women with heartburn were administered omeprazole 40 mg per day and TSH levels before and after six months of omeprazole treatment were then compared (3). While the patients in our study had hypothyroidism in reposition therapy, Centanni and cols. studied euthyroid women with atoxic multinodular goiter in suppressive therapy with the hormone. Another important difference was the duration of time that the hypothyroidism had been under control before omeprazole therapy was initiated. Centanni and cols. did not describe the period of time in which the patients had normal TSH levels before enrollment in the study. In our study, only patients whose TSH levels remained normal with stabilized doses of L-T4 for at least one year were selected. In our patients, the mean time of normal TSH levels was 5.5 ± 2.7 years for patients in the 20 mg group and 3.1 ± 1.7 years for patients in the 40 mg group. It is reasonable to believe that individuals experiencing hypothyroidism that is under control for a short amount of time are more susceptible to the development of TSH oscillations for reasons not related to proton-pump-inhibitor usage. In addition, these patients are more likely to be using inadequate doses of the hormone.

A clinical analysis based on a review of medical records found that the use of lansoprazole, which is another proton-pump-inhibitor, was associated with a slight increase in TSH levels in hypothyroid patients (5). However, the limitation of this study is that it was based on a retrospective analysis. Another possible explanation for the different result could be the use of a different proton-pump inhibitor. Although different medications of this class have the same effect on gastric pH, pharmacokinetic differences among them could lead to various drug interaction profiles. On the other hand, two pharmacokinetics studies evaluating the L-T4 absorption profile before and after the usage of different proton-pump-inhibitors (esomeprazole and pantoprazole) found no difference in the hormone kinetics, which is in agreement with our study (6,7).

Moreover, the hypothesis that pH interferes with L-T4 absorption has been speculated but not yet confirmed. It is known that aluminum hydroxide lowers L-T4 absorption, but *in vitro* studies have shown that it has a considerable capacity for adsorption of the hormone (2), which might be the mechanism involved in this interaction instead of its antacid effect. More

recent studies suggesting that patients with conditions associated with lower gastric acidity, such as atrophic gastritis (4) or *Helicobacter pylori* infection (3), need higher doses of L-T4 replacement reinforce the hypothesis that pH interferes with hormone absorption, but only in an indirect way. The interference of pH in the dissolution of L-T4 was objectively evaluated by Pabla and cols. in *in vitro* studies (8). In that study, which evaluated the brands Synthroid®, Tirosint® and generic levothyroxine, it was demonstrated that the higher the pH, the lower the L-T4 dissolution mean rate. However, the brand Tirosint®, a soft capsule, was minimally affected by pH, while Synthroid® exhibited the higher dependency on pH. The effect of pH on the three L-T4 products studied was different, even between Synthroid® and generic levothyroxine, which are both tablets. It is known that drug dissolution interferes directly with absorption and bioavailability. The fact that different L-T4 brand names are influenced by pH at different levels is a possible explanation for the disparities observed in the results of various studies evaluating the interaction of proton-pump-inhibitors and L-T4. In our study, all patients used the same brand name of L-T4 (Puran T4®).

It is possible that a slight interference caused by omeprazole in the action of L-T4 would be detected if the sample size had been larger. On the other hand, if this interference exists, it is not clinically significant for the group of patients with hypothyroidism in replacement therapy using adequate doses of L-T4.

Therefore, based on our findings, we believe that if a patient with hypothyroidism that has remained under control for the past year needs to start treatment with omeprazole, then there is no need to modify the reposition dose of L-T4. Even if this patient faces increases in TSH levels, it is important to rule out other causes before attributing it to the proton-pump-inhibitor.

Since levothyroxine reposition therapy has a narrow therapeutic window, it is crucial to identify factors that could influence its absorption, as either the excess or the deficiency of the hormone can lead to long-term complications. Recently, new L-T4 formulations have been developed (liquid and softgel), with the advantage of a more stable absorption profile and minimal dependence on intraluminal pH (9). In our country, however, the drug is only available in tablets. The development of new L-T4 formulations may have promising impact on the control of patients with hypothyroidism, especially in those with problems of impaired absorption.

Finally, more studies are needed for a better understanding of the gastric pH influence on L-T4 absorption and to explore the interaction of proton-pump-inhibitors and the hormone.

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