Levothyroxine absorption is not impaired in normal subjects treated short-term with gastric acid inhibitors famotidine or esomeprazole, or with ezetimibe


SUMMARY

BACKGROUND Gastric acid suppression is inconsistently reported to interfere with levothyroxine (L-T₄) absorption. This is a prospective study of the absorption of L-T₄ in normal volunteers taking famotidine, a histamine H₂ antagonist, esomeprazole, a proton-pump inhibitor, and ezetimibe, a lipid-lowering drug that inhibits intestinal absorption of cholesterol and related phytosterols. Ezetimibe was included in this study because the authors had preliminary information suggesting that the drug might interfere with L-T₄ absorption.

METHODS During the initial screening, 39 subjects with normal serum thyrotropin (TSH), thyroxine (T₄), triiodothyronine (T₃), free T₄, and free T₃ index levels were selected. Eligible subjects also had normal liver- and renal-function tests, a normal fasting gastrin level, negative Helicobacter pylori antibody titers, and normal hemoglobin; the women had a negative pregnancy test. Excluded were individuals with a history of thyroid disease, peptic ulcer disease, gastroesophageal reflux, erosive esophagitis, and erosive gastritis, or the current use of any drugs known to cause L-T₄ malabsorption. Nine subjects were excluded for various reasons. The 30 remaining study subjects were healthy, euthyroid volunteers who were assigned to one of three independent study groups, famotidine, esomeprazole, and ezetimibe (n = 10 in each group). In the three study groups, the mean (±SD) age was 28.1±3.1, 26.1±4.7 and 27.0±3.4 years, respectively, and the mean body weight was 139.9±8, 182.2±24.2 and 160.9±32.1 lb. Eleven were men and 19 were women, and the number of men and women in the three groups was 2/8, 4/6, and 5/5, respectively. At baseline, L-T₄ absorption was tested, followed by a 6-week washout period, after which a serum TSH was remeasured to reconfirm the subject’s euthyroid state. The final L-T₄ absorption test was performed approximately 1 week after the subjects were assigned to drug administration and immediately before the third and final L-T₄ absorption test. The study was performed as follows in the three study groups: 1 week of 20 mg famotidine (Pepcid) twice daily with meals, or 1 week of 40 mg esomeprazole (Nexium) daily with breakfast, or a single 10-mg dose of ezetimibe (Zetia). A 1-week administration of the gastric acid suppressive medications was selected to achieve a gastric pH >4 (range, 12 to 19). After an overnight fast, the L-T₄ absorption test was carried out with the administration of 600 µg of L-T₄ (Synthroid). Blood samples were obtained prior to and at 2, 4, 6, and 8 hours after L-T₄ administration. Mean and peak L-T₄ levels and calculated areas under the curve (AUCs) were obtained during absorption testing before and after study drug administration. In a secondary analysis, AUCs were compared using a subtraction model to correct for the baseline contribution of endogenous T₄ values from time zero before L-T₄ was administered. In another secondary analysis repeated-measures analysis of variance (ANOVA) testing was used to compare mean differences in hormone levels before and after administration of each study drug.

Figure 1. Mean peak serum thyroxine levels did not change significantly before and after famotidine (*P = 0.78), esomeprazole (**P = 0.52), or ezetimibe (***P = 0.46). All figures are adapted from data in Ananthakrishnan et al.

Figure 2. Mean serum thyroxine area under the curve did not change significantly before and after famotidine (*P = 0.53), esomeprazole (**P = 0.97), or ezetimibe (***P = 0.24) after t-test or ANOVA.
RESULTS Peak mean hormone levels and AUCs of $T_4$, $T_3$, and free $T_4$ ($FT_4$) and free $T_4$ index during the absorption testing before and after each of the three study medications did not differ significantly by paired t-test and ANOVA (Figures 1 and 2). Even when using the subtractive correction method of AUC, there were no significant differences before and after the administration of study medication (Figure 2). L-$T_4$ absorption did not change after a simultaneous dose of ezetimibe (Figure 1). After treatments with famotidine and esomeprazole, serum fasting gastrin levels were significantly higher than baseline levels as a result of gastric pH elevations (Figure 3), indicating compliance with the study medications.

CONCLUSION Short-term treatment with the gastric acid inhibitors famotidine and esomeprazole, and with ezetimibe, which inhibits intestinal absorption of cholesterol, does not affect L-$T_4$ absorption in healthy volunteers.

COMMENTARY

Approximately 62% to 82% of the oral dose of levothyroxine is absorbed by the intestinal mucosa, principally at the level of the upper jejunum and ileum (1), within the first and third hours (2) of ingestion. The rate of absorption can be estimated by the ingestion of radioactive iodine–labeled L-$T_4$ (3) or simply with large oral doses of L-$T_4$ in the range of 600 µg (4, 5). These observations have led to the discovery of a number of conditions that can lead to malabsorption of L-$T_4$, ranging from intestinal disease, timing of L-$T_4$ ingestion with meals, and the simultaneous use of drugs that inhibit L-$T_4$ absorption. In some ways, this study is a breath of fresh air because it found no impairment of L-$T_4$ absorption in healthy euthyroid subjects treated for 1 week with gastric acid inhibitors. Previous studies have shown that patients with impaired gastric acid secretion require an increased dose of L-$T_4$, suggesting that normal gastric acid secretion is necessary for effective absorption of oral L-$T_4$. Checchi et al. (7) recently reported that patients with hypothyroidism and autoimmune gastritis require larger than usual doses of L-$T_4$ to maintain the serum TSH in a normal range, which may be due to gastric mucosal atrophy. Still, this does not fully explain why L-$T_4$ absorption is impaired by gastric mucosal impairment, since most L-$T_4$ absorption occurs in the jejunum. The other drug studied by Ananthakrishnan et al. was ezetimibe, which targets the enterocytes at the small intestine brush border, blocking the absorption of biliary and dietary cholesterol from the small intestine by up to 50% or more, without blocking fat-soluble vitamins, bile acids, or triglycerides. The authors encountered a patient with primary hypothyroidism who was taking ezetimibe and required unusually large doses of L-$T_4$ to maintain the serum TSH in the normal range. However, this study shows that the drug did not impair L-$T_4$ absorption in normal subjects. Thus, all three drugs studied by Ananthakrishnan et al. did not impair L-$T_4$ absorption when given for a 1-week period.

Ernest L. Mazzaferri, MD, MACP

References