Give Levothyroxine Separately for Best Absorption

BY MICHELE G. SULLIVAN
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SAN FRANCISCO — A few hours' buffer between taking thyroxine and other medications can help ensure optimal absorption of the thyroid hormone, according to several researchers.

Many nutritional supplements and commonly prescribed medications interfere with thyroid absorption, the researchers said at the annual meeting of the Endocrine Society. When taken together, some medications bind the hormone so completely that virtually none enters the bloodstream.

"In most cases, it's believed that malabsorption of levothyroxine is due to binding of the hormone to other medications in the gut lumen, forming an insoluble or nonabsorbable complex," Dr. Steven P. Weitzman said in a poster presented at the meeting. Even newer compounds, which were thought to result in less malabsorption, seem to be problematic.

Dr. Weitzman, an endocrinologist at Stony Brook University, New York, examined the interaction of levothyroxine with two relatively new drugs—colesevelam (Welchol), the newest bile acid sequestrant approved for hyperlipidemia and diabetes; and lanthanum carbonate (Fosrenol), a new phosphate binder used in end-stage renal disease. The study included six healthy, euthyroid subjects, who first took levothyroxine 1 mg alone, then levothyroxine with 3.8 g colesevelam, then levothyroxine with 500 mg lanthanum carbonate. A minimum of 3 weeks separated each dosing study.

Total serum T_4 and TSH were measured at regular intervals during the 6 hours after administration of the study medications. Results were reported as both the area under the curve response and serum T_4 concentration.

Within 1 hour of taking levothyroxine alone, subjects displayed a sharp increase in serum T_4 from a mean of 7 mcg/dL to 10 mcg/dL. Serum T_4 peaked at 4 hours, reaching a mean level of 13 mcg/dL. The area under the curve response was 1,692 g-min/mL.

T_4 concentrations were significantly lower after the subjects took the hormone with lanthanum carbonate. At 1 hour, the T_4 level had risen to a mean of 8.6 mcg/dL. At 6 hours, the peak level was 11 mcg/dL. The area under the curve response was 982 g-min/mL.

Colesevelam exerted the largest inhibitory response on serum T_4. By 1 hour after taking the hormone and the medication together, mean T_4 levels rose to 7.6 mcg/dL and peaked there after 2 hours. The area under the curve response was only 107 g-min/mL.

"Both colesevelam and lanthanum carbonate reduced the absorption of levothyroxine and blunted the rise in serum T_4 when given with levothyroxine," Dr. Weitzman said. "Colesevelam appeared to be a particularly potent inhibitor of T_4 absorption and nearly abolished the increase in serum T_4.

In a second study, Dr. Bandar Alshehri, an endocrinology fellow at the University of Toronto, and colleagues performed a chart review of 549 hospitalized patients treated with levothyroxine during a mean 11-day hospital stay. Most of these patients (67%) were also receiving supplements or drugs known to inhibit the absorption of T_4. The offending compounds were proton pump inhibitors (42%), calcium supplements (28%), iron supplements (15%), multivitamins (13%), psyllium fiber (12%), and magnesium-containing antacids or laxatives (1%).

Most of the patients (97%) received their levothyroxine during the daytime; the majority (88%) also got their other medications during the same period.

Ninety percent of patients were getting the hormone within 1 hour of the potentially interfering medications. Fewer than 1% received the medications at least 4 hours apart. A simple change—routine administration of levothyroxine at bedtime—could reduce the offending coadministration rate to around 19%, because the interfering medications are not usually administered at bedtime, Dr. Alshehri said. ■

Subclinical Hyperthyroidism Elevates All-Cause Mortality

BY MICHELE G. SULLIVAN
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SAN FRANCISCO — A diagnosis of subclinical hyperthyroidism significantly increases the risk of death from any cause in the subsequent 10 years, especially among elderly patients, according to Dr. Patrick Haentjens.

The increased risk of death starts low and increases up until about age 80, with an overall increased risk of 41%, Dr. Haentjens said at the annual meeting of the Endocrine Society. After age 80, competing causes of death eliminate the association with thyroid dysfunction.

When translated to an absolute risk of death, excess mortality for a white U.S. woman diagnosed at age 70 was only 1.5% at 2 years, but increased to almost 9% by 10 years, said Dr. Haentjens of the Center for Outcomes Research, University of Ziekenhuis, Brussels. Men seemed to fare worse; for a white U.S. man diagnosed at age 70, the excess mortality risk was 2% at 2 years, 6% at 5 years, and almost 11% at 10 years after the diagnosis.

However, Dr. Haentjens' meta-analysis found no significantly increased mortality risk associated with subclinical hypothyroidism. The study was published online in the European Journal of Endocrinology (doi:10.1530/EJE-08-0110).

The meta-analysis included nine papers, which reported data on seven cohorts with subclinical hyperthyroidism (290 patients) and nine cohorts with subclinical hypothyroidism (1,580 patients). The individual studies compared long-term outcomes among these patients and 13,000 euthyroid controls. Follow-up ranged from 2 to 20 years.

Among the seven cohorts with subclinical hyperthyroidism, the hazard ratio for all-cause mortality ranged from 0.84 to 2.22. Only one paper (Lancet 2001;358:861-5) found a significant increase. However, in the pooled analysis, the overall risk was significantly increased, with a hazard ratio of 1.41, compared with euthyroid controls. Among the nine cohorts that explored all-cause mortality in patients with subclinical hypothyroidism, the hazard ratio ranged from 0.49 to 2. Three studies found significant differences, but one of them reported a significantly decreased risk of all-cause mortality, while the other two reported a significantly increased risk. Overall, the pooled analysis did not show an increased all-cause mortality risk. ■