Clin Thyroidol 2013;25:31–32.

Clinical THYROIDOLOGY
AMERICAN THYROID ASSOCIATION
FOUNDED 1923

Generic and Branded Levothyroxine Preparations Are Not Bioequivalent in Children with Congenital Hypothyroidism

Elizabeth N. Pearce

Carswell JM, Gordon JH, Popovsky E, Hale A, Brown RS. Generic and brand-name L-thyroxine are not bioequivalent for children with severe congenital hypothyroidism. J Clin Endocrinol Metab. December 21, 2012 [Epub ahead of print].

SUMMARY

Background

Generic substitution of levothyroxine (L-T_4) products determined to be bioequivalent by the Food and Drug Administration (FDA) is allowed in the United States. Bioequivalence is determined based on short-term pharmacokinetic studies of serum T_4 levels—and no assessment of chronic TSH responses—in healthy adult volunteers, a method that may not be adequately sensitive (1). It is known that in infants with severe congenital hypothyroidism, even small decrements in thyroid hormone may be associated with adverse developmental outcomes (2). Few clinical studies have been performed to date to determine whether generic and branded L-T_4 are truly bioequivalent in patients with hypothyroidism.

Methods

This was a prospective, unblinded, randomized, crossover trial. Study participants included 31 children and adolescents 3 to 18 years of age with known overt hypothyroidism (serum TSH concentration at diagnosis, >100 mIU/L). Twenty of the children had congenital hypothyroidism, while the rest had Hashimoto's thyroiditis with positive antithyroid antibodies. At baseline, all participants had maintained a normal serum TSH for at least 4 weeks on their usual L-T_4 formulation. Patients with gastrointestinal disease that could affect L-T_4 absorption or who were taking medications that could interfere with L-T_4 absorption or metabolism were excluded. One patient was excluded for failure to come to clinic visits. Participants were assigned to receive their usual L-T_4 dose as Synthroid (Abbott Laboratories) for 8 weeks and as the AB-rated generic (Sandoz) L-T_4 for 8 weeks; the sequence of the two treatments was randomly determined. Serum TSH, free T_4, and total T_3 at the end of each 8-week treatment period were compared for each subject. An intention-to-treat analysis was used.

Results

The serum TSH was significantly lower (0.7 mIU/L vs. 1.8 mIU/L, P = 0.002) after 8 weeks of Synthroid than after 8 weeks of the generic L-T_4; this difference remained significant after adjustment for age. Subgroup analyses determined that this difference was seen only in children with congenital hypothyroidism. In the children with Hashimoto's disease, TSH did not differ between branded and generic L-T_4. Results did not differ depending on whether generic or branded L-T_4 was administered first. There were no differences in free T_4 or total T_3 following each treatment period. Results did not differ when two patients who had been noncompliant with therapy were excluded from analyses.

Conclusions

This study demonstrates that Synthroid and generic Sandoz L-T_4 were not bioequivalent in children with congenital hypothyroidism, despite being deemed by the FDA to be interchangeable. The children with congenital hypothyroidism, at least 15 of whom had thyroid dysgenesis, may have been less able to compensate for a slight reduction in L-T_4 because of limited thyroid reserve.

continued on next page

ANALYSIS AND COMMENTARY

A major strength of the study was its prospective, randomized, interventional design. Study participants served as their own controls, which minimizes concerns about confounding. A limitation is the relatively small sample size; only 20 children with congenital hypothyroidism were studied.

Further research is needed to confirm these results and to determine whether they apply to other vulnerable populations, such as patients with athyreotic thyroid cancer. However, in light of these findings it would seem prudent to avoid substitution of L-T_4 products, especially in young children with severe congenital hypothyroidism and in other patients with hypothyroidism in whom alterations of the thyroid hormone level could have particularly deleterious effects. These data lend fresh support to the positions of the American Thyroid Association, The Endocrine Society, and the American Association of Clinical Endocrinologists that different L-T_4 formulations deemed interchangeable by the FDA may not be truly bioequivalent and that thyroid-function testing for dose titration is essential if formulations are changed (3).

References

1. Hennessey JV, Malabanan AO, Haugen BR, Levy EG. Adverse event reporting in patients treated with levothyroxine: results of the Pharmacovigilance Task Force Survey of the American Thyroid Association, American Association of Clinical Endocrinologists and The Endocrine Society. Endocr Pract 2010;16:357-70.
2. Salerno M, Militerni R, Bravaccio C, Micillo M, Capalbo D, Di MS, Tenore A. Effect of different starting doses of levothyroxine on growth and intellectual outcome at four years of age in congenital hypothyroidism. Thyroid 2002;12(1):45-52.
3. American Thyroid Association, The Endocrine Society, and American Association of Clinical Endocrinologists. Joint statement on the U.S. Food and Drug Administration's decision regarding bioequivalence of levothyroxine sodium. http://www.endo-society.org/advocacy/legislative/upload/Joint_Statement_Levothyroxine-Thyroxine.pdf.