

Levothyroxine dosage and the limitations of current bioequivalence standards

James V Hennessey

JV Hennessey is an Associate Professor of Medicine at the Brown Medical School, Rhode Island Hospital, Providence, RI, USA.

Precision in the dosing of levothyroxine (LT₄) products is guided by sensitive TSH measurements, and is essential to optimize therapeutic outcomes and assure patient safety. FDA regulation of LT₄ formulations aims to provide consistent drug content and bioavailability of the individual products approved for distribution in the US.^{1,2} What is unclear at this point, however, is whether true generic interchangeability among approved products has been achieved.

Once absorbed, orally dosed LT₄ exerts physiologic effects on metabolism, and a dynamic feedback effect on the hypothalamic–pituitary axis.³ In healthy individuals, the resultant modulation of the production and clearance of endogenous T₄ probably affects total circulating hormone levels. As LT₄ is converted to T₃ for therapeutic effect, measuring the concentration of the active ingredient (T₃) at the site of action—as is the intent of bioequivalence determinations—becomes impractical. In this situation, the quantification of total T₄ levels in the blood serves as the FDA-designated pharmacokinetic measure of choice.⁴

Precise and sensitive determination of therapeutic equivalence is important when comparing drugs acknowledged as having narrow therapeutic ratios.⁴ In a study of hypothyroid patients on optimal replacement therapy (mean dose 108 µg/day)—determined by their TSH response to TSH-releasing hormone—participants received a series of doses differing by up to 50 µg daily.⁵ When patients ingested 25 µg less than the optimal dose (a 0.23-fold difference), seven of nine patients (89%) were classified as hypothyroid. Conversely, when participants received 25 µg more than optimal (also a 0.23-fold difference), 11 of 20 (55%) of patients were classified as thyrotoxic.⁵ The 25 µg increment might be too large to reflect common clinical experience, however, as dosage adjustments of ≤12% are frequently made to achieve therapeutic goals.

The stated purpose of FDA bioequivalence evaluations is to demonstrate therapeutic consistency between preparations,⁴ which should ensure that substitution of products found to be

therapeutically equivalent can occur safely, and without the need for dose adjustment or follow-up therapeutic monitoring beyond that of the usual annual or semiannual interval. The choice of methods to document bioequivalence has recently been the subject of debate between clinicians and regulators.³ From a regulatory standpoint, the preferred method for documenting bioequivalence is the pharmacokinetic measurement of T₄ levels.⁴ The justification for this position rests on the understanding that measurement of the active ingredient at the site of action is not possible, and that some relationship exists between the efficacy and safety of the product and the concentration of the active moiety in the systemic circulation.⁴

A previous attempt to demonstrate bioequivalence uncovered discrepancies between the pharmacokinetic measures generated by clinical doses of LT₄ and the results of steady state TSH determinations.³ In standardized pharmacokinetic studies, ingested LT₄ is followed into the circulation, and levels of T₄ in the blood are measured for 48 h.³ Bioavailability is calculated from pharmacokinetic parameters, including maximum T₄ concentration (C_{max}) and the area under the T₄ curve observed over the 48 h period (AUC_{0–48}). Assessments are made for a name brand (reference) drug and the candidate generic formulation. Healthy volunteers ingest 600 µg doses of each product in a randomized cross-over manner, with 35-day wash out periods in between.⁴ Products are considered bioequivalent if the observed differences between the C_{max} values and the AUC_{0–48} values are insignificant. Statistically, the 90% CI of these differences must fall within 80–125% of the reference drug's value. This method should accommodate a 5% difference in each limit for a 10% total error;⁶ it is considered unlikely that generic products with bioavailability that differs by more than 10% could meet the CI requirements, and virtually impossible if the differences approach 20%.⁶ When initially introduced, correction for the endogenous T₄ pool was not required.^{7,8} Subsequently, the sensitivity of the original

Correspondence

Rhode Island Hospital—
Brown University
Hallett Center for Diabetes
and Endocrinology
1 Hoppin Street
Providence
RI 02903
USA
james_hennessey@
brown.edu

Received 30 November 2005

Accepted 12 April 2006

www.nature.com/clinicalpractice
doi:10.1038/ncpendmet0273

method to detect clinically relevant differences in absorbed LT_4 was assessed, found to be flawed,⁸ and a baseline correction method to account for endogenous T_4 was adopted in 2003.⁷ As a result, confidence has been established that differences in bioavailability of $\geq 25\%$ would be evident.⁸ Clinicians have questioned, however, whether differences of $< 25\%$ are reliably detected.

To allay these concerns, the FDA stated that differences in tablet content or bioavailability among therapeutically equivalent products should never exceed 9%, and the actual differences were more likely to average $\sim 3.5\%$, as reported for previously approved generic products.³ Clinicians agree that differences approaching 9% are clinically significant. Additionally, in the US, most clinicians recognize that differences of 9% exceed the increments of many currently available FDA-approved LT_4 doses. A difference of this degree would essentially render a prescription for 137 μg daily the equivalent of dispensing either 125 μg or 150 μg .

There are now four generic formulations and three reference preparations for LT_4 approved. Although the 90% CIs fall within the accepted limits, the arithmetic mean differences of the AUC_{0-48} reveal clinically significant variations. For example, the Sandoz generic LT_4 product is 12.5% more bioavailable than Synthroid[®] (Abbott Laboratories, Abbott Park, IL), but is 2.3% less bioavailable than Levoxyl[®] (King Pharmaceuticals, Bristol, TN).⁹ Synthroid[®] is 9% less bioavailable than the generic product from Mylan Laboratories, and 3% less bioavailable than LT_4 Lannett (the generic version of Unithroid[®], Jerome Stevens Pharmaceuticals, Bohemia, NY).⁹ Data on the relative bioavailability of the generic LT_4 product from Genpharm are not yet available.

These results have led the Endocrine Society, the American Association of Clinical Endocrinologists, and the American Thyroid Association into discussions with the FDA. The clinicians expressed concerns about the potential consequences of underdosage or overdosage of LT_4 , should products that differ as much as those outlined above be substituted for one another, and discussed alternative approaches to bioequivalence assessment.³ The suggested TSH standard was rejected by the FDA in May 2005, but the societies hope for further discussion of this concept.

In conclusion, the clinical community has welcomed the assurance of high quality LT_4 products through the FDA's new-drug application process.¹ These regulations require that the unique formulation of each product remains unaltered,

to assure consistent bioavailability. Each step of this standardization process has moved clinicians closer to the goal of enhanced patient care. The endocrine societies listed above have raised concerns that the sensitivity of the pharmacokinetic assessment methods for LT_4 bioequivalence could fall short of assuring that true interchangeability of products has been achieved. In the interim, the three societies have issued a joint statement that recommends maintaining patients on a consistent source of LT_4 by designating the brand name of the product given.¹⁰ Once generic substitution has occurred, refills with any of four formulations (three of which are rated as noninterchangeable with one another) are likely to occur. The societies suggest that patients should be educated to verify the LT_4 brand that they are prescribed. Patients are asked to note the tablet shape, color, and inscriptions to avoid unannounced substitution. The societies urge that additional serum TSH levels be re-evaluated after a 6–8 week equilibration period after any change in LT_4 source, to assess the need for retitration to maintain goal TSH values.¹⁰

References

- Hennessey JV (2003) Levothyroxine a new drug? Since when? How could that be? *Thyroid* **13**: 279–282
- US Department of Health and Human Services, FDA, and Center for Drug Evaluation and Research (2002) Guidance for industry: bioavailability and bioequivalence studies for orally administered drug products—general considerations [http://www.fda.gov/cder/guidance/4964dft.pdf] (accessed 19 July 2006)
- FDA (2005) Itinerary for the joint public meeting on equivalence of levothyroxine sodium products [http://www.fda.gov/ohrms/dockets/dockets/05n0137/05n-0137-1st0001.pdf] (accessed 19 July 2006)
- FDA (2005) Code of federal regulations, title 21, vol 5, subchapter D, part 320 [www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?CFRPart=320&show] (accessed 19 July 2006)
- Carr D *et al.* (1988) Fine adjustment of thyroxine replacement dosage: comparison of the thyrotropin releasing hormone test using a sensitive thyrotropin assay with measurement of free thyroid hormones and clinical assessment. *Clin Endocrinol* **28**: 325–333
- Henderson JD and Esham RH (2001) Generic drug substitution: issues for problematic drugs. *South Med J* **94**: 16–21
- FDA (2003) Advisory committee for pharmaceutical science 12–13 March 2003 [http://www.fda.gov/ohrms/dockets/ac/03/briefing/3926B1_01_H-FDA-Additional%20Information.doc] (accessed 19 July 2006)
- Blakesley VA *et al.* (2004) Are bioequivalence studies of levothyroxine sodium formulations in euthyroid volunteers reliable? *Thyroid* **14**: 191–200
- FDA (2006) Drugs@FDA [www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm] (accessed 19 July 2006)
- American Association of Clinical Endocrinologists, the Endocrine Society and the American Thyroid Association (2005) Joint position statement on the use and interchangeability of thyroxine products [http://www.thyroid.org/professionals/advocacy/04_12_08_thyroxine.html] (accessed 19 July 2006)

Competing interests

The author has declared associations with the following companies: Abbott Laboratories, Aventis, Novartis. See the article online for full details of the relationship.