



HYPOTHYROIDISM

EXPRESS REPORT™

Current Controversies in Thyroid Hormone Therapy

Based on Data Presented at a Continuing Medical Education Services Symposium during The Endocrine Society's 85th Annual Meeting June 20, 2003, Philadelphia, Pennsylvania

Expert Commentary

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It is widely appreciated that levothyroxine sodium preparations have a narrow therapeutic range, best assessed in patients with primary thyroid failure or following thyroidectomy by measuring the thyroid stimulating hormone (TSH) concentrations and not the serum free thyroxine concentrations. Thus a small change in the levothyroxine sodium dose, as little as 25 mcg daily, may result in an increase or decrease in the serum TSH concentration outside of the normal range, reflecting too little or too much replacement hormone, respectively. Even subclinical hypo- or hyperthyroidism can result in adverse systemic changes in a wide variety of peripheral tissues. For example, clinical experience has taught us that excessive levels of levothyroxine sodium are not benign and that over time, patients who receive too much thyroid hormone are at risk for osteoporosis, and adverse changes in cardiac function including arrhythmias. Also, the administration of doses of levothyroxine sodium that are insufficient may result in adverse changes in mentation, well being, serum lipid levels, and cardiac function. It is thus particularly important that the bioavailability of all levothyroxine sodium formulations be predictable, reliable, and consistent in order to minimize the risk of overdosing patients who require thyroid replacement or thyroid suppressive therapy.

To determine the bioavailability of levothyroxine sodium preparations, the United States Food and Drug Administration (FDA) requires the completion of pharmacokinetic studies.

However, these studies do not take into consideration the pharmacodynamic properties of the respective pharmacologic entities. Furthermore, studies are conducted in healthy volunteers, who are not representative of patients in whom the thyroid gland is absent or dysfunctional. Until very recently in testing levothyroxine sodium preparations, the FDA did not correct for basal thyroid hormone levels when calculating bioequivalence of levothyroxine sodium preparations.

It is for these reasons that the American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE) recommend that physicians use a single brand of levothyroxine sodium longitudinally, without cross-over between brands, in order to safeguard patients requiring thyroid hormone therapy from excessive or insufficient doses of hormone.

While common clinical practice is to suppress TSH values to undetectable levels in thyroid cancer patients, evidence now suggests that lower levels of thyroid hormone suppression may be considered in individuals who are free of disease 5 to 10 years after receiving treatment for thyroid cancer. In contrast, patients with evidence of persistent disease require more aggressive thyroid hormone suppression and TSH levels are still best left at undetectable limits.

Finally, controversy continues over the merit of replacing a proportion of standard levothyroxine sodium therapy with liothyronine therapy on the premise that therapy with only levothyroxine sodium results in hypothyroidism at the tissue level. However, studies exploring the benefit of liothyronine therapy have been less than convincing to date, and most experts still feel that liothyronine therapy has no long-term benefit and indeed may cause thyrotoxicosis over time.

Assessing Levothyroxine Sodium Preparations: Clinical Implications

As detailed by James V. Hennessey, MD, Associate Professor of Medicine, Brown Medical School, Providence, Rhode Island, earlier FDA guidelines failed to take into account basal thyroid hormone levels when calculating maximum concentrations (C_{max}) or area under the plasma drug concentration curve (AUC) following the oral administration of levothyroxine sodium preparations being tested for bioequivalence in euthyroid subjects.¹ As emerging data indicate, this could make a significant difference in the reliability of calculations to determine bioequivalence recommended by the FDA.

Because of concern that the FDA's approach to bioequivalence assessment might not be sensitive enough to detect differences in levothyroxine sodium preparations, a study was designed in which 36 healthy control subjects were assigned to three regimens of levothyroxine sodium in a fasting, open-label, randomized, three-period crossover study.² Levothyroxine sodium was given at a standard dose of 600 mcg (12 tablets Synthroid 50 mcg), at 450 mcg (9 tablets Synthroid 50 mcg) or a 25% reduction in the standard dose, and at 400 mcg (8 tablets Synthroid 50 mcg) or a 33% reduction in the standard dose.

"The same manufacturing lot of Synthroid was used for all three regimens," Dr. Hennessey noted, "[and the purpose was] to see if we have sufficiently sensitive methods to determine whether a given dose of levothyroxine sodium would fall within the range of variability permitted by the FDA, that is 80 to 125 percent." Uncorrected for baseline serum thyroxine concentrations, C_{max} and AUC for all three dosages fell within the FDA guidelines for approving a medication as therapeutically equivalent to a reference preparation, Dr. Hennessey observed.

However, when corrected for basal serum thyroxine levels, both C_{max} and the AUC fell outside the FDA-specified confidence interval for both the 25% reduction in dosage (450 mcg) and the 33% reduction in dosage (400 mcg). These findings prompted the FDA to change its standard approach for assessing bioequivalence between levothyroxine sodium preparations.

The issue of levothyroxine sodium bioequivalence has historically been confusing as illustrated by an example offered by Dr. Hennessey. A variety of therapeutic equivalence codes have been defined by the FDA and are intended to clarify for physicians and pharmacists those approved products which are, and are not, therapeutically equivalent. For example, "AB"-rated products are considered therapeutically equivalent; however, the "B" rating indicates that there may be potential bioequivalence problems. None of the branded preparations of levothyroxine sodium have been demonstrated to be therapeutically equivalent to each other and thus, are not interchangeable. The only generic levothyroxine sodium preparation that has received an "AB" rating from the FDA is manufactured by Mylan Laboratories and is interchangeable with only one branded levothyroxine sodium preparation (Unithroid).

Critically, however, therapeutic equivalence of this product was determined using the previous FDA standard for testing for bioequivalence (not subtracting basal serum thyroxine concentrations) that has been shown to be insufficient to detect differences in bioequivalence upwards of 25% to 33%. As importantly, the generic Mylan product was tested against only Unithroid and not against any of the other three currently available, branded levothyroxine sodium preparations. Therapeutic equivalence has therefore never been demonstrated between the generic Mylan product and any reference branded levothyroxine sodium preparation other than Unithroid. Anecdotally, it is believed that pharmacists are reading the "AB" rating of the generic Mylan levothyroxine sodium preparation as an "AB" rating that applies to every other branded levothyroxine sodium preparation—an interpretation that is both "inappropriate and inaccurate", as Dr. Hennessey noted, as the generic product was only compared to one reference drug (Unithroid).

Since the FDA has recognized that they must make adjustments in basal thyroxine levels for any generic drug approval process, Dr. Hennessey feels that some progress has been made in this regard. He went on to say that due to the New Drug Application (NDA) process that has been instituted by the FDA, currently marketed branded (BX rated) levothyroxine sodium preparations can be relied upon to provide adequate amounts of thyroxine as well as reasonable bioavailability but by FDA definition should not be substituted for one another.

Symposium Chair Leonard Wartofsky, MD, Professor of Medicine, Georgetown University, and Clinical Professor of Medicine, University of Maryland, Howard University and George Washington University Schools of Medicine, noted that clinicians still measure TSH to assess whether the thyroid hormone they are treating patients with is adequate, too little or too much.³

"The FDA criteria do not take TSH levels into account at all," noted Dr. Wartofsky. Furthermore, when proposing guidelines for conducting bioavailability studies, the FDA recommends measurement of only the rise in serum thyroxine following administration of a levothyroxine sodium preparation in normal volunteers, not in patients without a thyroid gland.

"This creates a number of confounding elements in assessing whether the compounds are truly bioequivalent," indicated Dr. Wartofsky. Indeed, the ATA and the AACE are concerned enough about the FDA's current recommended methodology for assessing bioequivalence that they have written a joint letter to the FDA urging them to reassess their current method for determining whether or not levothyroxine sodium preparations are bioequivalent, "because we think that minor differences in bioequivalence are critically important to our patients," as noted by Dr. Wartofsky.

Summarizing his thoughts on levothyroxine sodium therapeutic substitution, Dr. Wartofsky offered, "If one had a generic levothyroxine sodium product that was truly proven to be bioequivalent by rigorous standards, that would be fine. But, until

that is done, it is inherently risky to switch levothyroxine sodium preparations in individual patients.”

What Level of TSH Suppression is Optimal for Patients with Thyroid Cancer?

Until recently, it was generally felt that thyroid cancer patients should be maximally suppressed or at least be administered generous doses of thyroid hormone to ensure optimal clinical outcomes. With increasingly sensitive TSH assays, however, TSH levels that were once “undetectable” are now detectable despite having titrated the dose of levothyroxine sodium to achieve very low TSH levels, noted R. Michael Tuttle, MD, Memorial Sloan-Kettering Cancer Center, New York, New York.⁴ Driven by the need to avoid over suppressing patients and thus increasing the risk of adverse events, Dr. Tuttle reminded delegates that there has been a shift away from undetectable TSH levels towards sub-normal but detectable TSH levels over the past number of years.

In so doing, physicians need to know if lesser amounts of thyroid hormone adequately suppress thyroid cancer. According to a meta-analysis conducted by McGriff and colleagues,⁵ patients receiving thyroid hormone suppressive therapy had a lower risk of disease progression, recurrence, and death from thyroid cancer overall than those who did not. “Unfortunately, these were retrospective studies so they do not tell us what degree of TSH suppression was required [for improved clinical outcomes]” advised Dr. Tuttle.

One study in which TSH levels were evaluated indicated that patients with TSH levels <0.05 mIU/L had longer relapse-free survival rates compared to those whose TSH values were consistently >1 mIU/L.⁶ A separate group of investigators concluded that, based on an analysis of over 600 thyroid cancer patients, complete TSH suppression may not be needed in low-risk patients, although more aggressive suppression may be helpful in those at higher risk for disease recurrence.⁷

Dr. Tuttle also pointed out Burmeister and colleagues⁸ described four patients in which maximal thyroglobulin suppression was achieved with a TSH of 0.4 mIU/L. When the authors attempted to lower TSH levels further by increasing the dose of levothyroxine sodium, Dr. Tuttle reported that very little change was seen in the serum thyroglobulin. Dr. Tuttle observed, “This suggests that once you get down to a certain level of TSH, a lower TSH may not result in any further decrease in thyroglobulin.” Dr. Tuttle emphasized that it is still important to keep TSH levels in the sub-normal range in patients with thyroid cancer.

However, expert opinion suggests that TSH levels can be just at or below the normal range in low-risk patients. “The vast majority of patients with thyroid cancer should be maintained with TSH levels between 0.1 and 0.5 mIU/L and this gives optimal suppression of thyroglobulin and helps minimize whatever adverse events of over-treatment there may be,” stated Dr. Tuttle. But he also felt it was “perfectly acceptable” for some of the longest surviving, low-risk patients to have TSH values in the low-normal range.

On the other hand, undetectable TSH levels (TSH <0.1 mIU/L) are still preferable in patients with persistent thyroid cancer or high risk of recurrence or persistent measurable thyroglobulin, Dr. Tuttle added.

Benefits and Risks of Combined Levothyroxine/Liothyronine Replacement Therapy

E. Chester Ridgway, MD, University of Colorado Health Science Center, Denver, Colorado reviewed evidence both supporting and refuting the benefits of combination levothyroxine sodium/liothyronine replacement therapy as an alternative to standard levothyroxine sodium monotherapy.⁹ As Dr. Ridgway reminded delegates, “The ‘T₃ hypothesis’ suggests that peripheral conversion of thyroxine to triiodothyronine is inadequate and results in tissues which are deficient in triiodothyronine—a deficit which levothyroxine sodium therapy alone does not correct.”

But in fact, “Levothyroxine sodium therapy, which normalizes serum TSH, does normalize tissue triiodothyronine levels but also has high tissue thyroxine levels,” indicated Dr. Ridgway, citing results of a study conducted by Escobar-Morreale and colleagues.¹⁰ “Thus, levothyroxine sodium therapy that normalizes TSH produces a state of high, not low, tissue thyroid hormone levels,” added Dr. Ridgway.

The seminal study that raised the possibility that additional liothyronine therapy might lead to improvements in mood, cognitive function, and physical symptoms was carried out by Bunevicius and colleagues.¹¹ As that study reported, replacement of levothyroxine sodium 50 mcg with liothyronine 12.5 mcg improved cognitive performance (psychometric analysis) on 3 of 8 tests ($P<.05$); mood (psychometric analysis) on 4 of 9 tests ($P<.05$); mood (visual analogue scale) on 7 of 8 tests ($P<.04$); and physical symptoms (visual analogue scale) on 3 out of 7 tests ($P<.02$). These findings led the investigators to conclude that “partial substitution of liothyronine for levothyroxine sodium may have more salutary effects on the brain and perhaps other tissues than those of equivalent doses of thyroxine”.

As Dr. Ridgway went on to discuss, the Bunevicius study had methodological problems, not the least of which were the psychiatric outcomes used to assess the effect of the levothyroxine sodium/liothyronine approach are well validated for depression, but not for the diagnosis of hypothyroidism. The visual analogue scales upon which the authors assessed mood and physical symptoms were highly subjective and difficult for patients to interpret. The dose of liothyronine (12.5 mcg/day) was also a super-physiologic dose compared to what a normal thyroid gland secretes which is about 6 mcg/day, as Dr. Ridgway noted, and the timing of the testing following administration of the levothyroxine sodium/liothyronine combination coincided with the time serum triiodothyronine levels were peaking. Perhaps most importantly, the normal thyroxine: triiodothyronine molar ratio is 14 molecules of thyroxine to 1 molecule of triiodothyronine.¹²

“The molar ratio [in the Bunevicius study] was 8.5:1 and it was highly variable depending upon the initial levothyroxine sodium dose,” Dr. Ridgway noted, “which is far from being physiological.”

In a “purified sample” of the 26 women reported by Bunevicius et al,¹³ the previously observed differences in cognition, mood and physical symptoms in the two treatment groups no longer were significant in patients with Hashimoto’s thyroiditis when the groups were separated into those with Hashimoto’s thyroiditis and those with thyroid cancer. Furthermore, investigators from the Bethesda Naval Hospital also found no significant differences on a variety of outcomes between patients treated with a mean levothyroxine sodium dose of 129 mcg per day for 4 to 5 months and those in whom 50 mcg levothyroxine sodium were replaced with 15 mcg liothyronine.⁹

“The studies are better quality now and they are dealing with the appropriate ratio of thyroxine to triiodothyronine, but so far, it’s hard to say there is any benefit [to adding liothyronine],” Dr. Ridgway concluded. Dr. Wartofsky concurred, “I think what we are doing by adding liothyronine is that we are making patients mildly thyrotoxic for a short time, and they think they are feeling better. But if it is continued for a long time, there are adverse effects on bone and the heart. So, excess thyroid hormone, although it may make patients feel a little better in the short term, has adverse effects in the long term, and there are still no convincing or compelling data showing that adding liothyronine has any benefit.”

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