New Questions Regarding Bioequivalence of Levothyroxine Preparations: A Clinician's Response

Submitted: February 7, 2005; Accepted: February 7, 2005; Published: March 30, 2005.

William L. Green[1]

[1] Division of Endocrinology, Metabolism, and Nutrition, VA Puget Sound Health Care System, Seattle, WA 98108, and University of Washington School of Medicine, Seattle, WA 98195

ABSTRACT

A recent decision by the Food and Drug Administration (FDA) to declare various brands of levothyroxine bioequivalent has provoked objections from several physicians' organizations. These organizations assert that the method of testing bioequivalence is flawed, and that indiscriminate switching among preparations could lead to serious instances of undertreatment and overtreatment of hypothyroid patients. In this review we first list common indications for thyroid hormone administration, distinguishing its use as replacement therapy in hypothyroidism from its use to suppress thyrotropin (TSH) secretion in cases of thyroid cancer, nodules, and goiter. The dangers associated with changing to a preparation with different bioavailability are summarized, noting the particular danger of giving a more active preparation to a patient receiving TSH-suppressive doses of levothyroxine. However, these dangers are part of a larger problem: there are data showing that large numbers of patients are already receiving an improper dosage of levothyroxine, as judged from measurements of serum TSH. The recent history of FDA actions concerning levothyroxine bioequivalence and the arguments of those in disagreement are summarized. The immediate response to these problems should be better education of both patients and physicians. It is also recommended that there be further discussion of the problems in determining bioequivalence, and that consideration be given to more accurate and clinically relevant methods. Such methods should include assessment of the changes in TSH induced by each preparation in athyrotic patients.

INTRODUCTION

The recent decision of the FDA, to regard several brands of levothyroxine as bioequivalent, has the world of thyroid specialists up in arms. (The long history of levothyroxine use and FDA approval has been well covered by Hennessey.[1]) With this stamp of FDA approval, apparently it becomes legitimate for pharmacists to substitute among the "bioequivalent" drugs. Thyroid experts, however, are convinced that the method of determining bioequivalence is flawed, and that there may be important differences among preparations. If so, casually changing a patient to a new levothyroxine preparation could lead to over- or undertreatment, with possible adverse effects. An extreme case would be a change to a more potent preparation, causing atrial fibrillation and fatal embolism in a susceptible individual.

To consider this problem, we will first outline what are now the standards for levothyroxine therapy and consider factors that lead to a change in levothyroxine requirements. We shall then discuss how well these principles are being followed in practice, and how to meet the problem of changing to a preparation that may not be therapeutically equivalent.

Corresponding Author: William L. Green, 121 NW 171st Street, Shoreline, WA 98177. Tel: (206) 533-6320; Fax: (413) 254-9148; E-mail: annebillgreen@earthlink.net

CLINICAL USES OF LEVOTHYROXINE

Replacement Therapy in Primary Hypothyroidism

An excellent summary of the proper treatment of hypothyroidism was published more than 10 years ago,[2] and most of its recommendations are repeated in guidelines from the American Thyroid Association,[3] the American Association of Clinical Endocrinologists,[4] and the American College of Physicians in their PIER Web page.[5]

Briefly, the recommendation is that after the diagnosis of hypothyroidism has been confirmed by high serum levels of TSH and low levels of thyroid hormones, therapy should begin with levothyroxine. Younger patients (under 50) may start with a full replacement dose, 1.6 to 1.8 μg/kg body weight per day. Older patients, and patients with cardiovascular disease, are usually started at doses of 25 or 50 μg/day, increasing the dose at intervals. Treatment is monitored primarily by assessing the serum level of TSH; often assays of serum thyroxine (T4) or free T4 are also performed. Since levothyroxine has a long half-life, 7 days normally and longer in those with T4 deficiency, it is customary to monitor dosage at intervals of 6 weeks, and to adjust dosage until TSH is normalized. At this point usually the T4 concentration will be high normal, while the concentration of triiodothyronine (T3), the active hormone derived from T4, will be normal. Thereafter, follow-up at 6- to 12-month intervals is indicated.

There are several known factors that may require a change in dosage.[2] Certain drugs, including colestipol, cholestyramine, sucralfate, ferrous sulfate, aluminum hydroxide antacids, and calcium salts may interfere with absorption of levothyroxine;

this problem may be solved by taking levothyroxine at a different time from the interacting drug and readjusting dosage. Ingestion of soy protein, or a high-fiber diet, may also inhibit absorption. Other drugs, such as phenobarbital, the anticonvulsants phenytoin and carbamazepine, and the antituberculous agent rifampin can accelerate the metabolism of levothyroxine, necessitating an increase in levothyroxine dosage. Finally, dose requirements may slowly decline with age, may become greater if the patient develops celiac sprue or other causes of malabsorption, and are increased in pregnancy. Indeed, there is good evidence that the developing fetus may be harmed if maternal thyroxine levels are not well maintained in pregnancy.[6,7] All these situations should lead to more frequent monitoring of therapy. In the case of pregnancy, the common recommendation is that the dose be increased 30% in the first trimester, and then adjusted according to the TSH level.[8]

Two modifications or refinements of this practice have been suggested in recent years. One results from the claim that the truly normal range for TSH, and thus the therapeutic goal, is 0.5 to 2.5 mU/L, narrower than the 0.5 to 5.0 mU/L range reported as normal by many clinical laboratories. The arguments for this claim are that individuals with TSH values greater than 2 mU/L have a high incidence of later hypothyroidism, and that in populations rigorously defined as normal, the range of values is lower.[9] This finding supports the belief of many clinicians who felt that athyrotic patients were subjectively more content when TSH values were low normal. The second suggested change is based on the fact that in normal euthyroid individuals only 80% of the active hormone T3 is derived from peripheral deiodination of T4, while the remaining 20% comes directly from thyroid secretion. This has led some to advise that small amounts of T3 should be combined with T4 for more physiological replacement therapy. Use of T3/T4 combinations has allegedly had definite benefits compared with use of T4 alone, both anecdotally[10] and in one reported controlled study.[11] However, several further attempts to compare T4 alone to T3/T4 combinations have not been able to demonstrate any differences favoring the combination.[12-14] Although there may be more discussion of this question, at present the conclusion is that T3 coming from T4 is sufficient to restore euthyroidism, and that normal T3 production can be duplicated when T4 doses modestly exceed normal T4 production rates.

Replacement Therapy in Central Hypothyroidism

Although much less common than primary hypothyroidism, there are several patients who have thyroid hormone deficiency secondary to disease of the pituitary or hypothalamus. In these patients, the TSH level is not a reliable index of the adequacy of treatment, which must generally depend on restoring circulating levels of T4 and T3 to normal. The TSH level still may provide a clue. A recent study shows that the reciprocal relationship between T4 and TSH persists, and that hypopituitary patients adequately treated have low TSH levels.[15] Thus, a normal or elevated TSH suggests undertreatment.

Suppressive Therapy with Levothyroxine in Thyroid Cancer Patients

Many differentiated (papillary and follicular) thyroid cancers respond to TSH with an increase in radioiodine uptake and increased thyroglobulin secretion, indicating the presence of TSH receptors in tumor cells. Also, several retrospective studies have shown that recurrence of thyroid cancer after thyroidectomy is less frequent when patients are treated with levothyroxine, suggesting that cancer growth is partially TSH-dependent.[16] Thus, it has become common practice, after cancer eradication by surgery and radioiodine treatment, to give lifelong levothyroxine therapy. In high-risk patients, the goal may be a TSH level of less than 0.1 mU/L; lower-risk patients may receive levothyroxine doses that keep TSH near the lower limit of normal. In all cases, the possible benefits of tumor suppression must be weighed against the dangers of high thyroid hormone levels.

Suppressive Therapy of Goiter and Thyroid Nodules

At one time, thyroid hormone preparations were the standard therapy for thyroid enlargement and for thyroid nodules. Indeed, reductions in size were taken as evidence that a nodule was benign. However, in recent years, the efficacy of this treatment has been questioned. If there is evidence that a goiter is TSH dependent, such as being accompanied by a modest elevation of TSH, levothyroxine treatment may lead to shrinkage. However, nodules, whether single or multiple, seldom respond; also, the current approach to thyroid cancer depends on fine needle aspiration biopsy rather than on responses to levothyroxine treatment. When levothyroxine treatment is employed, however, again TSH is used to monitor therapy, and if suppressive levels of levothyroxine are employed, the risk:benefit ratio must be considered.

Consequences of Under- or Overdosage With Levothyroxine

The next question is, how serious are the effects of giving too much levothyroxine or too little in patients with compromised ability to secrete thyroid hormone? Or, using the TSH level as an index of under- or overtreatment, how big a change in T4 dosage is required to change the TSH to an undesirably low or high level? There have been several studies in which graded doses of levothyroxine were given and TSH measured. In one report, a 25-µg/day increment in dosage to patients with normal TSH caused the TSH of most subjects to fall to a mild-

ly subnormal level. Conversely, a decrease in dosage by 25 μg caused the TSH level in almost all subjects to reach levels above the normal range.[17] Clearly, any change in preparation that results in a change of 25 μg or more in effective dosage may push the TSH outside the normal range.

What, then, are the consequences of having a mildly abnormal TSH? There is now an extensive literature on so-called "subclinical hyperthyroidism" and "subclinical hypothyroidism," defined as an abnormal TSH with normal thyroid hormone levels. These studies document several pathological changes in lipid levels, cardiac function, and other parameters of thyroid hormone action. One caveat: several such reports do not distinguish spontaneously occurring subclinical disease from under- or overtreatment of hypothyroidism. Under stimulation, by either the abnormal stimulators that cause hyperthyroidism or the elevated TSH in hypothyroidism, the thyroid increases its output of T3, resulting in high T3/T4 ratios in serum. Conversely, T4 treatment decreases endogenous T3 formation, and the T3/T4 ratio falls with increasing levels of T4.[18,19] Thus, it is possible, particularly with reference to subclinical hyperthyroidism, that overtreatment with levothyroxine could differ from spontaneous mild hyperthyroidism.

In any case, the effects of overtreatment are small when TSH levels are between 0.1 and 0.5 mU/L, although there may be a modestly increased risk of atrial fibrillation, and adverse effects on patients with coronary disease. The risks are greater in the patient whose TSH has been suppressed to less than 0.1 mU/L, who have a greater chance of developing atrial fibrillation.[20] It has also been reported that such patients, after several years of treatment, have evidence of left ventricular hypertrophy and other cardiac abnormalities.[21] However, another group reports that these abnormalities can be corrected by lowering the levothyroxine dose to achieve a TSH just less than 0.1 mU/L.[22] Also, over long periods of time, particularly in older women, excessive thyroid hormone treatment is said to cause or aggravate osteoporosis.[23,24] Others have questioned this relationship,[25] and an increased incidence of fracture has not been documented.[26,27]

With regard to undertreatment, there is debate about the occurrence of serious consequences. TSH values up to 10 mU/L may have minimal effects, those being nonspecific symptoms and possible acceleration of atherosclerosis and heart disease. At higher TSH levels, hypercholesterolemia and other signs of hypothyroidism appear. There is one report from the Netherlands[28] describing increased occurrence of myocardial infarction in subclinical hypothyroidism, while a multiyear follow-up of patients with mildly elevated TSH levels showed no change in coronary artery disease.[29]

Attempting to put this all together, serious adverse effects of taking too much or too little thyroxine usually requires a change that would produce TSH levels less than 0.1 mU/L or greater than 10 mU/L.

How Often Do We Get It Right?

Obviously, with so many patients taking thyroid hormone medication, a certain number will be under- or overtreated. There are studies reporting that, in fact, a high proportion of those taking levothyroxine do have TSH values outside normal limits. In a survey performed in Colorado, many individuals were taking a thyroid hormone preparation; of these, 18% had low TSH values and 22% had high values.[30] In the National Health and Nutrition Examination Survey (NHANES), which attempted to test a cross-section of the United States population, among individuals who reported a prior diagnosis of thyroid disease 33% had abnormal TSH values,[31] similar to results of the Colorado study. Another study, examining TSH levels in the inhabitants of a small English town,[20] identified 61 individuals with a low TSH value (out of a total population of 2007), 36 of whom were taking thyroxine. In fact, of the 115 patients taking thyroid hormone, only 46 had TSH levels within the normal range.[20]

Thus, it is clear that many patients taking thyroid hormone preparations are not following the standard recommendation that dosage be adjusted every 6 to 12 mo to keep the TSH within normal limits.

How Does the Problem Concerning Bioequivalence Affect This Picture?

The FDA's judgment about bioequivalence is based on assays of total thyroxine in tablets, on studies of the speed of dissolution in vitro, and finally on in vivo studies of absorption and distribution. The in vivo study consists of determining serial T4 blood levels following administration of a standard large dose of levothyroxine, 600 μg, to normal subjects; the maximum T4 concentration achieved (C_{max}) and the area under the curve of serial T4 measurements (AUC) are then determined. When 2 preparations are to be compared, they are given, in a random crossover design, at least 35 days apart; then estimations of C_{max}, and AUC of the two preparations are compared. In the initial recommended protocol, no correction was made for endogenous T4 levels.[32] Then, a careful study by Abbott Laboratories, in which subjects were given 400, 450, or 600 μg T4, showed that the standard method could not distinguish among these doses (ie, could not distinguish a 33% difference [400 vs 600 μg], a 25% difference [450 vs 600 μg], or a 12.5% difference [400 vs 450 μg]). When a correction was made for the endogenous serum T4 concentration, the method could distinguish differences between the 600 μg and smaller doses, but not between the 400 and 450 μg doses. This study (which was later published[33]) was presented to the FDA Center for Drug Evaluation and Research (CDER) in May 2002. Subsequently,

a baseline correction was applied by CDER in the evaluation of a generic levothyroxine for which an abbreviated New Drug Application (ANDA) had been submitted, and it was shown that the corrected C_{max} and AUC still showed satisfactory agreement between the generic drug and a reference preparation of levothyroxine,[34] although the correction was not made part of policy. Some time later, in March 2003, when the data of the Abbott study were presented to the FDA Advisory Committee for Pharmaceutical Science, a baseline correction, subtracting the mean of 3 predose serum T4 assays from the T4 levels achieved after the trial dose, was accepted as the standard method for measuring pharmacokinetic parameters.[35] Also, since the earlier bioavailability protocols had included the collection of 3 baseline specimens, the modified calculations could be applied to studies already performed, and apparently all designations of bioequivalence are now justified by the newer calculations.[36] Some have continued to object even to these newer methods, pointing out that a variation in true bioavailability of up to 15% could be missed and urging the use of additional methods, particularly determinations of serum TSH levels in athyrotic individuals, to determine bioavailability—in other words, using the test most clinicians use to judge whether the proper amount of levothyroxine is being taken. After considering these arguments,[35] the FDA has decided that the combined set of requirements for bioequivalency, including both in vitro studies and the revised bioavailability protocol, are adequate. A joint statement from the Endocrine Society, the American Association of Clinical Endocrinologists, and the American Thyroid Association summarizes their objections to this action.[37] Both doctors and patients are advised to avoid changing the brand of levothyroxine taken, and to recheck TSH levels 6 weeks after any change in levothyroxine preparation.

In considering this problem, it is important to distinguish the hypothyroid patient whose TSH has been adjusted to the mid-normal range from one whose TSH is at the lower limit of normal. The patient with a mid-normal TSH is at the lowest risk; a 15% to 20% rise or fall in effective levothyroxine dose should seldom lead to a TSH far from the normal range and should not have immediate clinical consequences. Ideally, a checkup to reveal any change should be performed, but if this is not done, the change in TSH could be noted on the 6-month or yearly visit, and a change in levothyroxine dose recommended. However, the nearer the patient's TSH is to the upper and lower normal limits, the greater the risk that he or she will show adverse effects with such a change. Treatment of hypothyroidism during pregnancy is a special case, in view of the evidence that insufficient levothyroxine treatment over a short period of time may adversely affect the fetus.[7,8] It is essential that such patients be carefully monitored, and this would be a particularly bad time to change preparations.

There is greater concern about those in whom the TSH level is being deliberately suppressed to inhibit cancer growth or recurrence. There is some evidence that suppressing the TSH below 0.4 mU/L has no additional benefit in thyroid cancer patients.[38] However, in patients who are at high risk of recurrence, invasion, or metastasis, many recommend increasing the levothyroxine dose until the TSH is less than 0.1 mU/L, using an assay that can distinguish this from lower levels. This group is at high risk of adverse effects if they unknowingly are changed to a preparation with greater bioavailability.

As for those already receiving excessive doses as replacement therapy, there is a definite chance that changing to another preparation with greater bioavailability might lead to a more profound state of hyperthyroidism. Conversely, changing to a less bioavailable preparation, in a patient who is already undertreated, could aggravate the hypothyroid state. However, in these groups the first problem is a lack of informed medical care resulting either from patient inattention or caregiver ignorance; or, in the words of others: "In practice, most serious problems arise from flawed human behaviors, not improper drug formulation."[39] It seems likely that all physicians who become aware of this problem will first adjust the levothyroxine dose to a proper level, and then monitor the patient appropriately to compensate for changes in levothyroxine preparations that have different bioavailability, and for the several other factors that dictate a change in dosage. This does mean, of course, that the cost of managing and monitoring such patients will be higher than the cost of managing those who continue taking the same preparation.

Conclusion

The chief recommendation is that all physicians who prescribe levothyroxine be aware of both the standard of care in this area set by experienced physicians and the current problem with bioequivalence. If the standards of care are met, this should not only take care of the current concern over the FDA's action, but also the larger problem of improperly treated hypothyroidism. Also, the attempts should continue to accurately define levothyroxine bioequivalence, perhaps including TSH measurements in patients known to be athyrotic,[33] so that all concerned authorities can agree.

References

1. Hennessey JV. Levothyroxine a new drug? Since when? How could that be? *Thyroid*. 2003;13:279-282.

2. Mandel SJ, Brent GA, Larsen PR. Levothyroxine therapy in patients with thyroid disease. *Ann Intern Med*. 1993;119:492-502.

3. Singer PA, Cooper DS, Levy EG, et al. Treatment guidelines for patients with hyperthyroidism and hypothyroidism. Standards of Care Committee, American Thyroid Association. *JAMA*. 1995;273:808-812.

4. AACE Thyroid Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. *Endocr Pract*. 2002;8:457-469.

5. McDermott MT. American College of Physicians, Physicians' Information and Education Resource: Hypothyroidism. Available at: http://pier.acponline.org/physicians/diseases/d238/d238.html. Accessed September 20, 2004.

6. Pop VJ, Kuijpens JL, van Baar AL, et al. Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. *Clin Endocrinol (Oxf)*. 1999;50:149-155.

7. Haddow JE, Palomaki GE, Allan WC, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med*. 1999;341:549-555.

8. Alexander EK, Marqusee E, Lawrence J, Jarolim P, Fischer GA, Larsen PR. Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. *N Engl J Med*. 2004;351:241-249.

9. Baloch Z, Carayon P, Conte-Devolx B, et al. Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. *Thyroid*. 2003;13:3-126.

10. Arem R. *The Thyroid Solution.* New York, NY: Ballantine Books; 1999.

11. Bunevicius R, Kazanavicius G, Zalinkevicius R, Prange AJ, Jr. Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism. *N Engl J Med*. 1999;340:424-429.

12. Sawka AM, Gerstein HC, Marriott MJ, MacQueen GM, Joffe RT. Does a combination regimen of thyroxine (T4) and 3,5,3?-triiodothyronine improve depressive symptoms better than T4 alone in patients with hypothyroidism? Results of a double-blind, randomized, controlled trial. *J Clin Endocrinol Metab*. 2003;88:4551-4555.

13. Clyde PW, Harari AE, Getka EJ, Shakir KM. Combined levothyroxine plus liothyronine compared with levothyroxine alone in primary hypothyroidism: a randomized controlled trial. *JAMA*. 2003;290:2952-2958.

14. Walsh JP, Shiels L, Lim EM, et al. Combined thyroxine/liothyronine treatment does not improve well-being, quality of life, or cognitive function compared to thyroxine alone: a randomized controlled trial in patients with primary hypothyroidism. *J Clin Endocrinol Metab*. 2003;88:4543-4550.

15. Shimon I, Cohen O, Lubetsky A, Olchovsky D. Thyrotropin suppression by thyroid hormone replacement is correlated with thyroxine level normalization in central hypothyroidism. *Thyroid*. 2002;12:823-827.

16. McGriff NJ, Csako G, Gourgiotis L, Lori CG, Pucino F, Sarlis NJ. Effects of thyroid hormone suppression therapy on adverse clinical outcomes in thyroid cancer. *Ann Med*. 2002;34:554-564.

17. Carr D, McLeod DT, Parry G, Thornes HM. Fine adjustment of thyroxine replacement dosage: comparison of the thyrotrophin releasing hormone test using a sensitive thyrotrophin assay with measurement of free thyroid hormones and clinical assessment. *Clin Endocrinol (Oxf)*. 1988;28:325-333.

18. Lum SM, Nicoloff JT, Spencer CA, Kaptein EM. Peripheral tissue mechanism for maintenance of serum triiodothyronine values in a thyroxine-deficient state in man. *J Clin Invest*. 1984;73:570-575.

19. Nicoloff JT, Lum SM, Spencer CA, Morris R. Peripheral autoregulation of thyroxine to triiodothyronine conversion in man. *Horm Metab Res Suppl*. 1984;14:74-79.

20. Sawin CT, Geller A, Wolf PA, et al. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. *N Engl J Med*. 1994;331:1249-1252.

21. Biondi B, Fazio S, Carella C, et al. Cardiac effects of long term thyrotropin-suppressive therapy with levothyroxine. *J Clin Endocrinol Metab*. 1993;77:334-338.

22. Mercuro G, Panzuto MG, Bina A, et al. Cardiac function, physical exercise capacity, and quality of life during long-term thyrotropin-suppressive therapy with levothyroxine: effect of individual dose tailoring. *J Clin Endocrinol Metab*. 2000;85:159-164.

23. Greenspan SL, Greenspan FS. The effect of thyroid hormone on skeletal integrity. *Ann Intern Med*. 1999;130:750-758.

24. Ross DS, Neer RM, Ridgway EC, Daniels GH. Subclinical hyperthyroidism and reduced bone density as a possible result of prolonged suppression of the pituitary-thyroid axis with L-thyroxine. *Am J Med*. 1987;82:1167-1170.

25. Toft AD. Clinical practice. Subclinical hyperthyroidism. *N Engl J Med*. 2001;345:512-516.

26. Solomon BL, Wartofsky L, Burman KD. Prevalence of fractures in postmenopausal women with thyroid disease. *Thyroid*. 1993;3:17-23.

27. Bauer DC, Ettinger B, Nevitt MC, Stone KL. Risk for fracture in women with low serum levels of thyroid-stimulating hormone. *Ann Intern Med*. 2001;134:561-568.

28. Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, Witteman JC. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. *Ann Intern Med*. 2000;132:270-278.

29. Tunbridge WM, Evered DC, Hall R, et al. Lipid profiles and cardiovascular disease in the Whickham area with particular reference to thyroid failure. *Clin Endocrinol (Oxf)*. 1977;7:495-508.

30. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. *Arch Intern Med*. 2000;160:526-534.

31. Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab*. 2002;87:489-499.

32. Food and Drug Administration. Center for Drug Evaluation and Research. Guidance for Industry: Levothyroxine Sodium Tablets–In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing. Available at: http://www.fda.gov/cder/guidance/3645fnl.htm. Accessed March 8, 2000.

33. Blakesley V, Awni W, Locke C, Ludden T, Granneman GR, Braverman LE. Are bioequivalence studies of levothyroxine sodium formulations in euthyroid volunteers reliable? *Thyroid*. 2004;14:191-200.

34. Yu LX. Letter to ANDA file: Approval of ANDA 76-187, Mylan Pharmaceuticals Inc, Levothyroxine Sodium Tablets. Available at: http://www.fda.gov/cder/foi/anda/2002/076187_Bioequiv_Corresp.pdf. Accessed June 5, 2002.

35. Food and Drug Administration. Advisory Committee for Pharmaceutical Science. Record of Proceedings. Available at: http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3926T2.pdf. Accessed November 15, 2004.

36. Hubbard WK. Request that the Commissioner of Food and Drug take action described methodology for oral levothyroxine sodium drug products: Reply to Petitioners. Available at: http://www.fda.gov/ohrms/dockets/dailys/04/June04/062904/03p-0387-pdn0001-vol5.pdf. Accessed June 23, 2004.

37. American Thyroid Association, The Endocrine Society, American Association of Clinical Endocrinologists. Joint statement on the U.S. Food and Drug Administration's decision regarding bioequivalence of levothyroxine sodium. *Thyroid*. 2004;14:486.

38. Burmeister LA, Goumaz MO, Mariash CN, Oppenheimer JH. Levothyroxine dose requirements for thyrotropin suppression in the treatment of differentiated thyroid cancer. *J Clin Endocrinol Metab*. 1992;75:344-350.

39. Oppenheimer JH, Braverman LE, Toft A, Jackson IM, Ladenson PW. A therapeutic controversy. Thyroid hormone treatment: when and what? *J Clin Endocrinol Metab*. 1995;80:2873-2883.