



Thyroid Roundtable: The Clinical Implications of Recent Research

Program Overview

An estimated 13 million people in the United States are currently being treated for thyroid disorders. Thirteen million more Americans may have undiagnosed thyroid dysfunction. Studies indicate that people with thyroid dysfunction face an increased risk for adverse cardiovascular, neuropsychiatric, and pregnancy outcomes.

A majority of people diagnosed with thyroid disease are prescribed levothyroxine sodium (LT₄), a synthetic version of the endogenous thyroid hormone, which has a narrow therapeutic range. A careful approach to therapy and an understanding of bioequivalence and therapeutic equivalence are essential when using LT₄, especially in certain high-risk patients, such as patients with thyroid cancer, pregnant women, and the elderly.

This activity provides an in-depth discussion of the risks associated with untreated thyroid disease and the need to carefully calibrate LT₄ therapy in patients. In addition, the standards used to determine the bioequivalence and therapeutic equivalence of LT₄ products and the need to understand the importance of determining equivalence when prescribing LT₄ therapy are discussed.

Target Audience

This activity is designed for endocrinologists, primary care physicians, and family physicians interested in the treatment of patients with thyroid disorders.

Educational Objectives

Upon completion of this educational activity, participants will be able to

- Summarize the risks associated with untreated thyroid disease and the potential adverse events associated with over- and underdosing of LT₄.
- Define bioequivalence and therapeutic equivalence.
- Discuss issues that complicate the assessment of the bioequivalence of various LT₄ preparations.
- Recognize patient types that require careful calibration of LT₄ therapy.

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Introduction

One in 10 Americans has thyroid disease. Many of those affected rely on levothyroxine sodium (LT₄) therapy to maintain the correct level of thyroid hormone and to ensure proper functioning of major organs and body systems. Approximately 13 million people take LT₄ preparations daily. In caring for these patients, physicians must individualize the dosage of LT₄ in each patient to achieve a narrow therapeutic range of thyroid-stimulating hormone (TSH). Issues of the bioavailability and bioequivalence of LT₄ products can complicate dosing. A recently completed study indicated that the procedures the US Food and Drug Administration (FDA) has used to measure the bioavailability of LT₄ products are flawed.¹ The results of this study were presented at an FDA meeting in March 2003.

Leonard Wartofsky, MD, MPH, MACP, professor of medicine, anatomy, physiology, and genetics, Uniformed Services University of the Health Sciences, professor of medicine, Georgetown University School of Medicine, clinical professor of medicine, Howard, Maryland, and George Washington Universities, chairman, Department of Medicine, Washington Hospital Center, is an endocrinologist and leading expert on thyroid disease. Dr Wartofsky presented a clinical context for this study when it was presented to the FDA. He later joined with several experts in this field to discuss the important clinical implications of this study. The participants in this roundtable were the following individuals: **Stephen Brunton, MD**, director of faculty development, Stamford Hospital/Columbia University Family Practice Residency Program; **Michael Katz, PharmD**, clinical associate professor of pharmacy practice and science, University of Arizona College of Pharmacy; **E. Chester Ridgway, MD**, professor of medicine and head of the Division of Endocrinology, Metabolism and Diabetes at the University of Colorado Health Sciences Center; and **Joseph E. Scherger, MD, MPH**, family physician.

This panel began their discussion by reviewing a case report that illustrated the problems that can occur when patients are switched from one LT₄ product to another. The group then discussed the following topics:

- The importance of precise dosing of LT₄
- Patient populations in which precise calibration of LT₄ therapy is crucial
- How bioequivalence is assessed
- The recent study evaluating the criteria used by the FDA to assess the bioequivalence of LT₄ products
- The implications of this study for clinical practice

- The substitution of LT₄ products at the pharmacy
- Issues associated with substitution of generic LT₄ products for brand-name LT₄ products

Case Report

A 51-year-old woman visited her physician for an annual physical. She was diagnosed with Hashimoto's disease at age 46, based on the finding of an elevated serum TSH level and positive antithyroid antibodies. She was prescribed 100 µg/d of a brand-name LT₄ product. Yearly monitoring showed her TSH level to be within the target therapeutic range of 0.5 to 2.0 mIU/L that is supported by many authorities. This year, however, her TSH level had increased to 12 mIU/L, and her free thyroxine (FT₄) level had decreased from 2.0 to 1.2 ng/dL.

The patient was asked about compliance with prescribed medications and the possible use of any additional medications that could interact with LT₄. She denied any compliance or interaction problems. She was asked to repeat the TSH testing, which yielded a serum TSH level of 15 mIU/L. Her LT₄ dose was increased to 125 µg/d.

She returned for testing 2 months later, which showed her serum TSH to be 9 mIU/L. She was asked to return with all her medications. It was found that her pharmacy had substituted her brand-name LT₄ with a generic formulation. She was switched back to the brand-name drug at a dosage of 100 µg/d. On testing 2 months later, her TSH level had declined to 1.8 mIU/mL.

Why Precise Dosing of Levothyroxine Sodium Is Important

Dr Wartofsky: Dr Ridgway, how would you characterize what occurred in this case?

Dr Ridgway: In this case, the fact that the patient was switched from one brand of LT₄ to another preparation that was apparently subpotent allowed her TSH level to dramatically increase, leaving her hypothyroid. It took 2 office visits and 3 TSH tests to remedy the situation, which added expense and time to her treatment.

Dr Brunton: As primary care physicians, we often spend a lot of time trying to stabilize a patient's TSH level in the target range. This can be very difficult. Once you think you have the TSH level stabilized, you often find that control has been lost and then realize, as in this case, that the patient has been switched from one brand to another or to a generic LT₄. It is difficult to titrate patients, but when you are treating peo-

ple in whom a delicate balance becomes a critical issue—for example, if they have comorbid conditions—it can be very challenging.

Dr Wartofsky: As endocrinologists, we are concerned about LT₄ dosing because we feel that minor changes in LT₄ preparations can have highly significant clinical effects in our patients. Either a slight overdosage or underdosage of LT₄ is associated with demonstrable clinical effects, which may not be apparent in the short term, but which are apparent with chronic use. Given that most of our patients are chronically taking LT₄, these are real problems.

In the context of inaccurate or imprecise dosing, we need to consider both over-replacement—when a particular LT₄ tablet contains a greater amount of drug than is stated on the bottle—and under-replacement—where the tablet contains less drug than the stated dose.

Overdosage produces effects on the heart and on bone, resulting in atrial fibrillation, tachyarrhythmias, and bone loss (Table 1). We have empirical models for that, without exogenous thyroxine administration, as reported by Sawin et al² in the Framingham population. In this group, minor degrees of TSH level suppression that were related to endogenous mild hyperthyroidism (also known as subclinical hyperthyroidism), were associated with more than a 3-fold increased risk of atrial fibrillation.² With atrial fibrillation comes the associated risk of thromboembolism, stroke, and rate-related congestive heart failure due to the rapid rate of the atrial fibrillation. In fact, a low serum TSH concentration (<0.5 mIU/L) in individuals 60 years of age or older is associated with increased mortality from all causes, and from cardiovascular mortality in particular.³

Table 1. Potential Consequences of Overdosing and Underdosing of Levothyroxine Sodium

Overdosing
Accelerated bone loss
Fractures
Atrial fibrillation
Symptoms of hyperthyroidism
Underdosing
Return of symptoms of hypothyroidism
Return of associated adverse health effects
Elevated total cholesterol and LDL cholesterol
Impaired cognition
Inadequate TSH suppression in patients with thyroid cancer

LDL, low-density lipoprotein

The second area of concern involves the effects on bone. We know that chronic long-term excessive use of LT₄ will result in osteopenia and osteoporosis.^{4,5} Patients with hyperthyroidism can actually present with fractures due to osteoporosis, so physicians are concerned that years or decades of slight overdosage of LT₄ could have similar effects.

In the context of underdosage, physicians need to remember that they are treating patients for hypothyroidism. If they are not receiving enough LT₄, they are going to continue to be hypothyroid and have the symptoms and signs that warranted the therapy in the first place. Although the thyroxine is being replaced, it is an inadequate amount, so such patients may suffer from subclinical hypothyroidism, also called mild thyroid failure. We know that the consequences of subclinical hypothyroidism can include impaired cognition and effects on serum cholesterol, low-density lipoprotein cholesterol (LDL-C), and other lipid moieties that are related to atherosclerosis with increased risk of atherogenesis, plaque formation, coronary artery disease, and myocardial infarction.

A patient does not need to have overt hypothyroidism to have these potential risk factors. Years or decades of mild underdosage caused by an inadequate amount of LT₄ could produce some of these highly undesirable adverse effects.

Dr Ridgway: I agree. If you are treating a patient with cardiovascular problems and he or she is given a sub-potent LT₄ preparation so that the thyroid levels decrease and the cholesterol levels increase, then you are putting the patient at risk (Figure 1). And if you completely suppress the TSH level with an overly potent medication, the chance of arrhythmias or other kinds of tachyarrhythmic problems is increased.

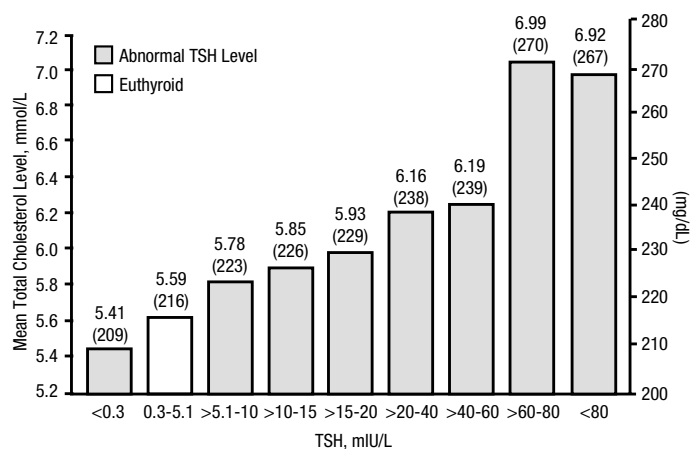


Figure 1. Total cholesterol levels in 25 862 subjects according to serum TSH levels. All mean cholesterol levels are significantly different from the mean cholesterol level of the euthyroid participants.⁶

If you are treating a patient with cardiovascular problems and he or she is given a subpotent LT_4 preparation so that the thyroid levels decrease and the cholesterol levels increase, then you are putting the patient at risk.

Dr Wartofsky: There are certain categories of patients in whom the effects of underdosage would be highly undesirable (Table 2). This would include pregnant patients, where subclinical hypothyroidism is associated with the offspring having a significantly lowered IQ compared with control children from normal mothers. In patients with thyroid cancer, we want to prescribe a highly specific dosage of LT_4 , which is targeted to bring the patient's TSH level to a desirably suppressed range. Thus, if the tablet does not contain what we expect it to contain, then the TSH level will be inadequately suppressed. TSH is a mitogen, or growth stimulant. It will stimulate any residual thyroid cancer cells to grow and multiply, and the patient will present with a worsening of his or her underlying malignancy. We have a goal to keep the TSH at a specific level in patients with thyroid cancer.

If we administer too much LT_4 , this will lead to adverse effects on the heart and bone. Too little LT_4 will allow the thyroid cancer to flourish. Therefore, it is very important for the dosing to be very tightly regulated, and endocrinologists rely on a highly precise dosage form to achieve the desired tight control. They expect the tablet to have the correct amount of LT_4 , which will create the desired therapeutic outcomes in the patient.

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Dr Ridgway: This brings us to the question of how the FDA determines the bioequivalence of generic drugs in general, and LT_4 bioequivalence in particular. Dr Katz, could you review for us the criteria used to judge whether a generic drug is bioequivalent to a brand-name drug?

Table 2. Populations in Which Precise Levothyroxine Dosing Is Imperative

- Pregnant women
- Thyroid cancer patients
- Elderly patients
- Patients with heart disease

How Bioequivalence Is Assessed

Michael Katz, PharmD: The FDA defines bioequivalence in terms of the relative bioavailability of 2 products. Bioavailability is a measure of the rate and extent of a drug's absorption. After administering the drug and measuring the active ingredient in plasma, a concentration-time curve is generated. The C_{max} (the concentration at which the level in the bloodstream is highest) represents the rate of absorption. The area under the curve (AUC) describes the extent of absorption.

For bioequivalence assessment, we compare the AUC and C_{max} of the time-concentration curve for a reference formulation (the brand-name drug) to that of the test formulation (the generic), as shown in Figure 2. We are trying to decide if these 2 curves are statistically identical or statistically different. For a generic drug to be deemed bioequivalent to a reference drug, both the AUC and C_{max} must meet the following criteria: the 90% confidence interval for the generic must lie between 80% and 125% of that of the reference drug, using log-transformed data and applying a 2-sided statistical test (Figure 3).

Dr Scherger: Are these the criteria the FDA uses in bioequivalence testing of all drugs?

Dr Katz: For all oral drugs. They have used these criteria for testing thousands of products, and they have worked well. For most drugs, this range of bioequivalence is not a problem. It is with the narrow therapeutic index drugs (a drug requiring careful dose titration and monitoring) that physicians may not believe these

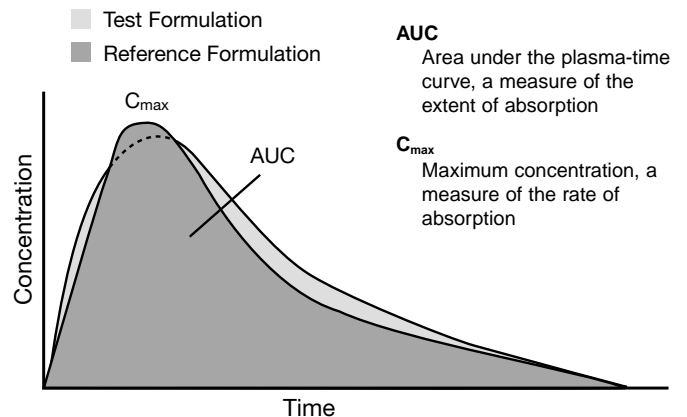


Figure 2. Bioequivalence assessment is done by comparing pharmacokinetic parameters.

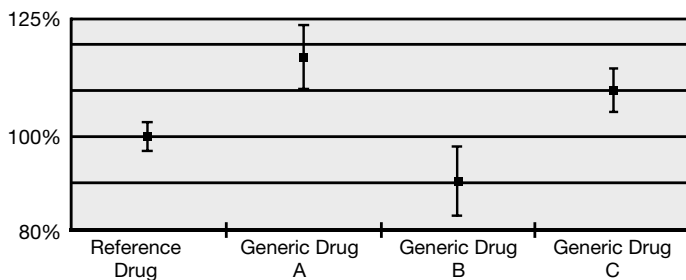


Figure 3. Generic drugs may vary from 80% to 125% of the reference drug and still be declared bioequivalent.

criteria are relevant. The FDA recognizes that LT_4 is a narrow therapeutic range drug; nevertheless, they specify the standard bioequivalence criteria will be used.⁷ The bioequivalence standards still are the traditional 80% to 125%.

Dr Scherger: I think most physicians would be alarmed at the allowed range of variability—80% to 125% of the reference product. If the patient is experiencing that kind of variability as they go from one product to the next, their control is not going to be assured.

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Dr Katz: Indeed, a 25- μ g dose change of LT_4 is within that FDA definition of what would be equivalent—that range of 80% to 125%. And a 25- μ g dose change is enough to change a patient from being euthyroid to being either hypo- or hyperthyroid, as a study by Carr and colleagues showed.⁸ [\[\[hyperlink: Carr D, et al study\]\]](#)

Also, these pharmacokinetic studies done to determine bioequivalence as mandated by the FDA are done in healthy volunteers. The assumption is that what happens in healthy volunteers is the same as what happens in patients. For many drugs, that may be true, but in a complex system, such as thyroid disease, this is not always true. Many of us would question whether single-dose pharmacokinetics in healthy volunteers tells us much about what dynamically occurs in patients with thyroid disease.

Dr Wartofsky: Also complicating the assessment of bioequivalence of LT_4 products is the fact that LT_4 is not a drug, per se, but is a synthetic form of a naturally occurring substance in the body.

Dr Katz: Yes. Exogenously administered LT_4 hormone is indistinguishable from endogenously secreted T_4 , both in its physiologic effects and its quantification as measured in blood. In healthy volunteers, there is some blood level of T_4 before the dose of LT_4 is given for the pharmacokinetic study.

In fact, endogenous T_4 accounts for approximately 70% of the AUC in pharmacokinetic studies, meaning that the majority of what we are calculating in comparing 2 different products is based on the patient's endogenous T_4 level rather than what we are pharmacologically administering. And from patient to patient, there is a substantial variability in their baseline level.

Therefore, in a pharmacokinetic study with a small number of patients, those differences could be significant. Should we be correcting for that endogenous amount, performing a baseline correction? When bioequivalence calculations were made in the past, that baseline endogenous amount was not accounted for; the assumption has been that it does not matter.

Recent Study on Levothyroxine Bioequivalence Testing

Dr Wartofsky: For all these reasons, I have had concerns about the FDA's approach to assessing bioequivalence of LT_4 preparations.^{9,10} It was with great interest that I noted that Abbott Laboratories had done a study this past year that tested the appropriateness of the current FDA guidance for bioequivalence assessment.¹ They did the study according to FDA guidelines recommended for such studies.

Levothyroxine sodium was administered to 33 healthy, normal volunteers using a randomized, 3-way crossover protocol with the appropriate washout period. Subjects were fasting. Rather than comparing a generic drug to a reference drug, they gave subjects 3 different doses of Synthroid[®], using tablets from one lot: 600 μ g (twelve 50- μ g tablets), 450 μ g (nine 50- μ g tablets), or 40 μ g (eight 50- μ g tablets). The study assessed whether the FDA criteria could distinguish between a 600- μ g versus a 450- μ g versus a 400- μ g dose in normal volunteers.

[\[\[hyperlink: Synthroid bioequivalence assessment \[study \[abstract\]\]\]](#)

Dr Wartofsky: One could not distinguish between these doses by using the current pharmacokinetic criteria that are employed by the FDA. The problem, as we have been discussing, is that these normal individuals have a large amount of endogenous or baseline T_4 production from their thyroid glands. Until now, the FDA has not agreed to any form of baseline correction to eliminate this substantial contribution to the T_4 lev-

els that are present during such studies. I believe they are reconsidering this approach and will agree to some baseline correction in the future; however, they still rely on pharmacokinetic criteria—AUC and C_{max} —rather than looking at pharmacodynamic criteria (the effect of the LT_4 on the patient as measured by the TSH response to treatment).

As clinicians, we assess therapeutic efficacy by looking at the serum TSH level. The serum TSH concentration has been accepted for years as the gold standard of thyroid hormone effect in the body **[[hyperlink: TSH]]**, and we now have highly sensitive, accurate, reproducible, third-generation TSH assays that can measure an individual's response to a dose or doses of LT_4 . However, the FDA bioequivalence criteria do not consider TSH concentration, but simply measure T_4 concentration. It is well known that many things can affect serum T_4 concentrations and alter study results.

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Dr Ridgway: That is why in the clinical environment, the test of bioequivalence is not the T_4 level but the TSH level.

Dr Brunton: Absolutely, that is the measurement we use in terms of stabilization of thyroid function.

Implications of the Study

Dr Brunton: Let's discuss the important clinical implications of the study.

Dr Wartofsky: It was a well-done, well-controlled study, and it met all the standards recommended by the FDA. What the study shows is that the current FDA criteria will not accurately assess bioequivalence and that products can have a variance of between 12% and 33% that will not be detected by these criteria (Figure 4).

That means we may be prescribing LT_4 preparations that vary so much that they could cause our patients to develop subclinical hypothyroidism or subclinical hyperthyroidism.

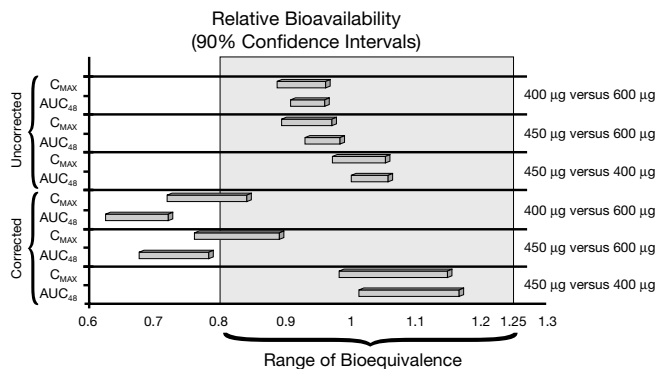


Figure 4. Study results. Doses that differed by as much as 33% (400 µg versus 600 µg) would pass the FDA criteria for bioequivalence (eg, uncorrected for endogenous thyroxine; 90% CIs with the 80% to 125% range). Even when corrected for endogenous T_4 , doses differing by 12.5% (400 µg versus 450 µg) would still satisfy bioequivalence requirements.

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Dr Ridgway: As we have discussed, it does not take a major change in LT_4 dose to move a patient from being euthyroid to being either hypo- or hyperthyroid. **[[hyperlink: Summary of Carr study]]** But the most important implication of the study in my view was the fact that almost any dosage can pass the criteria that the FDA has implemented when you do not do a baseline correction.

Dr Scherger: The message of the study for primary care physicians is that they need to insist on a specific brand of LT_4 and make sure that they have a clear communication with the pharmacist that the prescription should not be changed. The patient should have the same understanding, so the patient can be aware of the pills that are being prescribed and know that once he or she is stabilized on a dosage or given a certain treatment, he or she needs to remain on that prescribed medication.

The message of the study for primary care physicians is that they need to insist on a specific brand of LT₄ and make sure that they have a clear communication with the pharmacist that the prescription should not be changed.

Substitution of Levothyroxine Products at the Pharmacy

Dr Katz: This study provides further evidence that switching among the different LT₄ products, even those few that are considered bioequivalent or AB-rated by the FDA [\[hyperlink: FDA's Orange Book\]](#), would not be in the patient's best interest.

One thing that prescribers need to be aware of is that, even in states where substitution among products is controlled [\[hyperlink: State regulations on substitution\]](#), substitution of LT₄ products does occur. Often the prescriber is not aware when patients are being switched from one LT₄ product to another.

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One thing that prescribers need to be aware of is that substitution of LT₄ products does occur. Often the prescriber is not aware when patients are being switched from one LT₄ product to another.

Dr Brunton: This is true. Often when you order a branded LT₄ drug and the patient gets a generic substitution, you may never be aware of it, unless the patient brings the pills into your office.¹¹

Dr Katz: Much of that switching is due to pressure by managed care organizations on the dispensing pharmacy.

Dr Scherger: Yes. Substitution at the pharmacy is a very old issue, but right now there is a tremendous assertiveness in controlling drug costs, even for pennies, which leaves the doctor and the patient less powerful in ensuring that they are getting exactly what they want.

Dr Katz: If you want to be sure that the product you are prescribing is the product that the patient receives at the pharmacy, then you should (1) discuss that issue with the patient, making sure the patient is aware that you do not believe generic agents are equivalent to the agent you are prescribing; and (2) make sure that if you write a prescription for a brand-name product that you write "dispense as written" or "do not substitute" or whatever your state regulations mandate to ensure that what you are prescribing is what is dispensed.

Dr Scherger: That is important. Otherwise, pharmacists may be able to substitute a variety of different products for a patient, which may not have direct correlation to what the physician prescribed. It is very important that once the patient is stabilized, or even while you are adjusting the dosage, that you are consistent with the product being used and do not have this added variability.

There are some health problems where switching brands or generics is not nearly as important as it is in titrating a drug in which dosage changes need to be fine-tuned. I think that treating with LT₄ is probably the best example of the need to fine-tune a drug.

Assessing Bioequivalence

Dr Wartofsky: I am a supporter of having inexpensive preparations of LT₄ available; however, the major caveat is that they have to be truly bioequivalent. I would like any product on the market to be exactly equivalent to any other product, irrespective of whether they are branded or generic. If any product could meet true criteria for bioequivalence in a well-controlled study, this would be highly acceptable. The problem is we currently do not have a means of assessing bioequivalence.

We in the endocrine community are urging the FDA to consider convening a panel of experts to draft improved guidelines for assessing the bioequivalence of LT₄ products.¹² The Endocrine Society, the American Thyroid Association, and the American Association of Clinical Endocrinologists have volunteered to provide such experts to the FDA. We would certainly hope that they would agree to do that.

In the meantime, the American Thyroid Association, the American Association of Clinical Endocrinologists, and the American College of Endocrinology have recommended that patients be treated with branded LT₄ products rather than generic products, and maintained on the same brand of LT₄ throughout treatment.^{13,14}

The endocrine community is urging the FDA to consider convening a panel of experts to draft improved guidelines for assessing the bioequivalence of LT₄ products. In the meantime, the American Thyroid Association, the American Association of Clinical Endocrinologists, and the American College of Endocrinology have recommended that patients be treated with branded LT₄ products rather than generic products, and maintained on the same brand of LT₄ throughout treatment.

Dr Scherger: There are contrary views—the idea that all generic products are equal and that with the current FDA policies, we do not have a lot to worry about using generic products.

Dr Brunton: That is true. For example, the American Academy of Family Physicians' position paper on generic drugs states that FDA-approved generic medications are reasonable alternatives to brand-name medications, and that concerns about bioequivalence have largely been resolved.¹⁵ But I do not think most people understand the variability that you can have with generic products. People assume that if it is a generic, it is the same thing as the brand-name drug, and do not recognize the confidence limits of equivalency. With a drug such as an antibiotic, these confidence limits may or may not make much of a difference. But they do with metabolic medications and with medications that have a narrow therapeutic index, such as LT₄.

As we have seen, the range of latitude in potency that the current guidelines allow can negatively affect the stability of a patient's treatment of a thyroid disorder.

Dr Scherger: Right. As we have seen, the range of latitude in potency that the current guidelines allow can negatively affect the stability of a patient's treatment of a thyroid disorder.

Summary

Dr Ridgway: There are serious health consequences to both overtreating and undertreating hypothyroidism. Very small changes in an LT₄ dosage can have major implications for the patient's level of control and the

TSH level. Too much LT₄ causes osteoporosis and a faster heart rate, which is especially serious in the elderly. Undertreated hypothyroidism also has major health effects.

Dr Brunton: Although it appears that treating hypothyroidism is simple, because the treatment is only 1 medication, the fine-tuning for adequate control is a delicate process. It should not be tampered with every time the patient goes to the pharmacy to get thyroid medicine.

Dr Katz: It is clear that the standards the FDA has been using to compare LT₄ product bioequivalence are not adequate and could not distinguish between different doses. This could introduce a great deal of variation in a patient's therapy, as demonstrated in the case study.

Dr Scherger: It is very important that the product being used is consistent and not have this added variability. To maintain that consistency, physicians need to insist on a specific brand of LT₄ and make sure that it is not changed.

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Dr Wartofsky: I believe there is consensus among us on that point. As physicians, we would like to feel confident that when we prescribe a dose, our patients are getting that dose. Given that the current FDA criteria would not accurately assess bioequivalence and that products can have a significant variance that will not be detected by these criteria, we must protect our patients by insisting on a consistent brand of LT₄.

Link: Impact of Small Changes in Levothyroxine Dose on Thyroid Control:

Carr et al Study

Dr Ridgway: A study by Carr and colleagues⁷ showed that small changes in the dose of LT₄ can have a major effect on a patient's TSH control (Figure 5). In this study, the researchers treated 21 hypothyroid patients until they were euthyroid. Their doses were then adjusted in 25- μ g increments, and T₄ and T₃ levels, both free and bound, and TSH levels, were measured. With a 25- μ g increase, 55% of the patients had an abnormally low TSH level and were biochemically hyperthyroid. When the dose was lowered by 25 μ g, almost all of the patients became hypothyroid based on TSH level criteria. Very small doses had a very large impact on the TSH level.

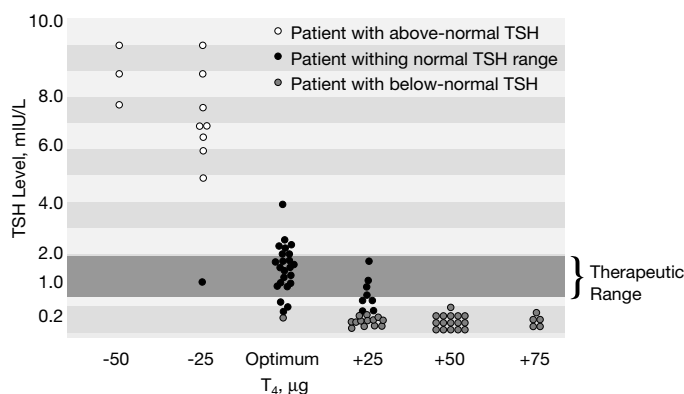


Figure 5. The effect of small changes in LT₄ dosage. A 25- μ g change in dose resulted in an abnormal TSH concentration for the majority of patients.⁸

Given that the FDA criterion for bioequivalence of generics is 20% below to 25% above the values of the brand-name reference drug, the 25- μ g dose change in the Carr et al study is within that FDA definition of equivalence. So, dose changes within the FDA criteria of bioequivalence in fact had a tremendous impact on the patient's biochemical thyroid state.

Link: Thyroid-stimulating Hormone (TSH)

Dr Wartofsky: A TSH level remains our window into the body. It is the most precise way we have of assessing whether patients are euthyroid or not. It is hard to measure a thyroid hormone effect in the liver, kidney, brain, or muscle, but we can measure in the pituitary because we have this highly sensitive marker, TSH, which tells us when levels are a little too high or a little too low. We refer to this as the “thyrostat” and we rely on it. If we had an approved method of assessing bioequivalence that incorporated TSH measurements—the true pharmacodynamics of T₄ bioequivalence—then I think we as endocrinologists would feel significantly more assured that when we prescribe LT₄

to our patients, they are truly getting the dose we want them to get, irrespective of the brand of the thyroxine that is given.

Link: The FDA's Orange Book and Drug Substitution

Dr Katz: The FDA publishes its therapeutic equivalence ratings in *Approved Drug Products With Therapeutic Equivalence Evaluations*, often referred to as the *Orange Book* because of the color of its cover.¹⁶ Drugs that the agency considers to be therapeutically equivalent are given an “A” rating; those not considered equivalent are rated “B.”

Currently (May 2003), the *Orange Book* lists 7 LT₄ products. Only 2 of these—Unithroid[®] and a generic LT₄ produced by Mylan Laboratories, Inc.—have an “AB” rating, which means that, in the FDA's view, any bioequivalence problems have been resolved, and these 2 products are officially eligible for substitution.¹⁶ The other LT₄ products are coded “BX,” which indicates that equivalence has not been determined.

Link: State Regulations on Substitution of Drugs

Dr Katz: Substitution of one drug for another by pharmacists is governed differently in each state. In most states, pharmacists may substitute only those products rated “A” in the *Orange Book*.¹⁶ **[[hyperlink: FDA's Orange Book]]** In other states, there is a formulary of products that may (positive formulary) or may not (negative formulary) be substituted. “Professional judgment” states allow a licensed pharmacist to use his or her professional judgment regarding the interchange of drugs.

Different states also mandate different language for protecting prescriptions from generic substitution. Depending on your state regulations, if you write a prescription for a brand-name product, you need to write “dispense as written” or “do not substitute” or whatever your state regulations mandate to make sure that the drug you are prescribing is one that is dispensed.

Link: Synthroid Bioequivalence Assessment Study

Abstract

Objective: To test the sensitivity of the current FDA bioequivalence methodology by evaluating how much 2 formulations could differ and still pass these bioequivalence criteria.

Design, Setting, and Participants: Randomized 3-period crossover trial in healthy euthyroid volunteers between 19 and 50 years of age.

Interventions: Subjects were administered LT₄ 600 µg (twelve 50 µg tablets), 450 µg (nine 50 µg tablets), and 400 µg (eight 50 µg tablets). Tablets from a single lot of Synthroid were used. Each subject was given each dosage; a washout interval of at least 44 days separated the doses.

Main Outcome Measures: Total T₄, total T₃, and TSH were measured at intervals from 30 minutes before to 96 hours after dosing. Maximum serum concentration (C_{max}), time to C_{max}, and area under the serum concentration-time curve (AUC) were estimated for total T₄ with and without correction for endogenous T₄.

Results: A total of 33 subjects (16 men, 17 women) were included in the pharmacokinetic analyses. Without correction for endogenous T₄, all 3 tested doses of LT₄ (600 µg, 450 µg, and 400 µg) would be declared bioequivalent. With baseline correction, the methodology could distinguish 600 µg from 450 µg and from 400 µg, but 400 µg and 450 µg would still be declared bioequivalent.

Conclusions: The pharmacokinetic criteria that have been used by the FDA to assess the bioequivalence of LT₄ products cannot distinguish dose differences of up to 33% (400 µg versus 600 µg). Even after correcting for endogenous T₄, these criteria cannot distinguish doses that differ by 12.5% (400 µg versus 450 µg).

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