Evaluation of Bioequivalence and Efficacy of L-thyroxine Preparations in the Treatment of Human Thyroid Disease

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7 February 2003

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1. INTRODUCTION

Human thyroid disease is a health issue of great magnitude. Current estimates suggest that 10 to 12 million Americans are diagnosed with hypothyroidism and treated with various formulations of thyroid hormone replacement.[1] Optimum therapy requires precise replacement of the deficiency in thyroid hormone production, which results from a variety of primary thyroidal diseases.[2] Good clinical management of these patients requires thyroid hormone replacement doses that are precisely titrated both to avoid persistent hypothyroidism and prevent unwanted iatrogenic hyperthyroidism[3] with the resulting deleterious cardiac and metabolic effects.[4] Variations in drug dosage of as little as 15% can result in changes in serum TSH which, if lowered in older patients, can result in atrial fibrillation.[3] Therefore, in the choice of thyroid hormone replacement pharmaceutical products it is necessary to understand the drug formulation, its dissolution, absorption, transport to sites of action, metabolism, and clearance, as well as the methods by which such parameters should be measured and compared.[5] Previous studies have looked at a variety of pharmacokinetic and bioavailability issues which relate to L-thyroxine therapy.[6] This review will highlight those and emphasize the importance of comparing and contrasting preparations, with potentially differing clinical efficacy, in patients receiving thyroid replacement rather than in euthyroid normal volunteers where seemingly small, yet clinically significant, differences in therapeutic effect may be overlooked.

2. THYROID HORMONE PHYSIOLOGY

Starting with the 12th week of gestation the human thyroid gland is formed and initiates production of thyroid hormone. After extracting iodine from blood against a concentration gradient and under the regulation of thyroid stimulating hormone (TSH) the thyroid gland accomplishes a number of energy requiring metabolic steps which couple iodine to a tyrosine molecule and then subsequently synthesizes both L-thyroxine (T_4) and 3,5,3'-triiodothyronine (T_3).[7] The majority of hormone (85%) is produced in the thyroid gland as T_4 and only a small amount as T_3. It is well established, however, that T_3 is the biologically active form of the hormone.[8] It is the form of hormone which binds to specific nuclear receptors and exerts cellular action on every tissue and organ in the body.[9] By the second and third trimesters, the majority of T_4 originates within the fetal thyroid. After birth the hepatic and renal enzymes, which metabolize T_4 to T_3 by monodeiodination, are matured and normal levels of T_4 and T_3 are established.

As a result of the ubiquitous action of T_3 on essentially every cell type in the body, the symptoms of thyroid hormone deficiency (hypothyroidism) are clearly separate and distinct from those seen in the euthyroid state.[10] Hypothyroidism, which most commonly arises as a result of autoimmune destruction (chronic lymphocytic thyroiditis) of the thyroid gland, gives rise to a progressive decrease in the ability of the gland to synthesize and secrete L-thyroxine.[11] The symptoms of hypothyroidism are well established and include those changes in normal physiology, which would be predicted to arise from a decrease in the rate of cellular metabolism in each and every organ system. These symptoms include:

- a decrease in basal metabolic rate,
- decrease in body temperature,
- bradycardia,
- decreased cardiac contractility,
- decreased cardiac output,
- increased systemic vascular resistance,
- slowed mentation, and
- decreased hepatic synthesis of various important proteins including clotting factors, and impaired renal function - ultimately leading to coma and death.[2]

The signs of hypothyroidism are well known and the diagnosis can be confirmed in essentially every case by measurements of the serum levels of T_4, T_3, and most importantly, TSH. [12] In general, the severity of the clinical symptoms of hypothyroidism are proportional to the degree of impairment of thyroid gland synthetic function as reflected by serum measures of T_4 and T_3, and most importantly, by the rise in serum TSH. However, it has also been observed that both the age of the patients and the duration of symptoms are important in determining the magnitude of the clinical signs and symptoms.[2]

Hyperthyroidism occurs when the production of thyroid hormone by the thyroid gland is supra normal.[13] This can occur for a variety of reasons, including Graves' disease, toxic multinodular goiter, toxic follicular adenoma, subacute thyroiditis, or more importantly, for the purpose of this discussion when the dose of thyroid hormone used for treatment of hypothyroidism is in excess (iatrogenic hyperthyroidism). The signs and symptoms of hyperthyroidism are basically diametrically opposite to that of hypothyroidism.[12,13] They include weight loss in the face of an increased caloric intake, heat intolerance, tachycardia, enhanced cardiac contractility, decreased systemic vascular resistance, irritability, sleep disturbance, emotional lability and in its most severe forms, fever, delirium and cardiovascular collapse resulting from thyroid storm.[2]

3. L-THYROXINE REPLACEMENT FOR HYPOTHYROIDISM

The history of thyroid hormone replacement for hypothyroidism dates back to the observation made in the late 19th century, when partially purified extracts of bovine thyroid gland were given to patients with classic signs and symptoms of hypothyroidism, their clinical symptoms improved. In view of the fact that these patients suffered from severe disease, it was relatively easy to establish a clinical response to treatment. However, the response was quite variable and in some cases iatrogenic hyperthyroidism resulted. Almost two decades later the active ingredient T_4 and later T_3 in thyroid gland extracts were identified. This led to the synthesis of L-thyroxine and its use in the treatment of hypothyroidism.[14] At the present time, synthetic preparations of L-thyroxine are the standard treatment for primary hypothyroidism. Previous therapies, including the use the of animal thyroid extract, the combination treatment of T_4 and T_3, as well as the single use of T_3, have fallen into disfavor because of the lack of standardization for animal formulations, the widely

differing half-lives between T_4 and T_3, and the observation that in the majority of patients with primary hypothyroidism, T_4 is converted to T_3 at a rate sufficient to establish a euthyroid state.[15]

The normal adult thyroid gland produces approximately 90 to 100 mcg of thyroid hormone per day while in children, thyroid hormone production is directly related to body mass. After total thyroidectomy, the replacement dose of thyroid hormone is fairly standard at 1.6 mcg/kg with the total varying from 100 to 200 mcg per day. T_4 replacement is accomplished by the use of single daily oral doses of L-thyroxine which has a half-life of seven days. A steady state of hormone replacement is reached 4 to 6 weeks after T_4 dose adjustment.[16] Patient to patient L-thyroxine replacement doses vary due to a variety of individually specific variables. These include body mass, the degree of absorption (individual GI motility, food effects, GI disease states, and interfering drugs and minerals) metabolic conversion of T_4 to T_3 primarily by the Type I 5'monodeiodinase in the liver, renal clearance of hormone, and to some degree the level of thyroid hormone binding globulins in serum (TBG).

4. ASSESSMENT OF THYROID HORMONE REPLACEMENT

Today the primary laboratory test used for the assessment of the adequacy of thyroid hormone replacement is the serum TSH level.[16] Prior to the late 1980's, the sensitivity of the TSH assay (first generation) was limited to values within the normal range and thus was used primarily for the detection of hypothyroidism.[5] Now, TSH assays (third generation) are much more sensitive with accuracy down to 0.01 to 0.02 mU/L.[17] Current third generation assays are sensitive enough to allow the precise titration of thyroid hormone suppressive therapy in thyroid cancer patients and also to permit careful monitoring of TSH levels in L-hyroxine replacement patients where the avoidance of low TSH levels is desirable.[3,18]

5. TREATMENT OBJECTIVES

There are several issues that must be considered when establishing a normal population or individual patient TSH range. First, secretion of TSH is pulsatile with a diurnal rhythm. Serum TSH levels peak at night and fall to half that level during the day.[19] However, apart from diurnal variation, euthyroid individuals have a very narrow range of TSH levels when monitored during the day. Second, most hypothyroid patients are women whose estrogen and progesterone cycles affect the binding capacity of thyroid hormone. Thus, in premenopausal female patients there may be additional variability in free hormone and TSH levels despite consistent sampling times.

Taking into consideration all of the above, an appropriate range of "normal" for TSH in patients receiving L-thyroxine replacement should be revisited. The lower limit of normal has been reported as 0.3 to 0.5 mU/L and the upper limit as 3.9 to 5.5 mU/L.[17] Healthy euthyroid individuals have a median serum TSH value of 1.5 mU/L and since 95% of these individuals have values under 2.5 mU/L, the "true" normal range may be narrower than currently suggested.[20] In turn, there may be risks attached to values which fall below this

level.[3,18,21] TSH values above 0.1 mU/L but not exceeding 0.4 mU/L are "slightly low," and values between 2.5 and 5.0 mU/L, previously considered normal, may be "slightly elevated." As a result, the target range for patients on L-thyroxine replacement therapy may be more narrowly defined and precise dosing of L-thyroxine replacement enables tighter control of TSH levels in patients. Small dose adjustments e.g., <20% of the daily dose may cause the patient to respond with TSH outside normal limits.[22]

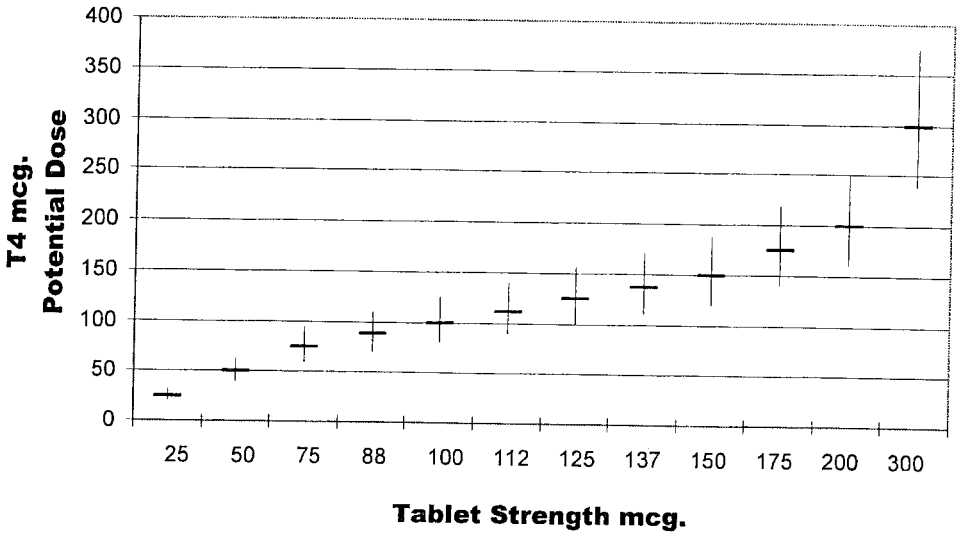
There is evidence that patients with low TSH levels as the result of excessive L-thyroxine treatment are at increased risk for cardiovascular disease especially atrial fibrillation.[3,21] It is important to prevent these unwanted effects by understanding L-thyroxine pharmacokinetics and the measures of cellular hormone action.[23] After reaching steady-state conditions, typically 4-6 weeks after starting or changing L-thyroxine dosing, TSH measurements are the standard for determining whether the patient is receiving the proper thyroid hormone replacement dosage.[5] The effectiveness of treatment can be ascertained at the end of that period of time by measuring serum TSH as well as clinical assessment of thyroid hormone action at which time modification of replacement dosage can be made.[23]

In response to step-wise increases in L-thyroxine replacement dosage there is a progressive and predictable decline in serum TSH.[2,24] Adequate and appropriate replacement has historically been defined when serum TSH has returned to levels within normal population range.[20] As noted above, the ideal post-treatment TSH level may be even more narrowly defined. This also produces normal levels of serum T_4 and T_3 in the majority of patients.[16] Lastly, the clinical euthyroid status of such patients can be confirmed using a variety of physiologic parameters including basal metabolic rate, resting heart rate, thyroid symptom rating scales[25] measures of lipid metabolism, specifically cholesterol, and measurements of a variety of thyroid hormone sensitive cellular enzymes including erythrocyte sodium-potassium ATP-ase and muscle creatine kinase.[2,23] Patients can be identified as properly treated when serum TSH is normal, and clinical signs and symptoms of hypothyroidism have resolved.[10,23,25] After establishing a clinically and chemically euthyroid status this can be maintained by periodic evaluation of thyroid hormone blood levels and by avoidance of a variety of confounding variables which can alter the potency or efficacy of L-thyroxine replacement therapies. These changes most likely arise from alterations in bioavailability. Thus it is important to establish that individual L-thyroxine preparations have reliable and reproducible bioavailability based upon established criteria for dissolution, absorption and *in vivo* drug metabolism.

6. BIOAVAILABILITY

Under current standards for bioequivalence of T_4 formulations, treatment doses of T_4 are considered approvable and equivalent if the patient exposure falls within 80%-125% of the dose administered as a solution of an equivalent T_4 dose.[26] While this equivalence is only tested at a single 600 mcg dose in normal healthy volunteers, the standard is applied across all dosage strengths. According to this rationale, current standards call for the equivalency doses that are 80%-125% of the label as reflected below.

Labeled Dose (mcg.)	80% x Dose (mcg.)	125% x Dose (mcg.)
25.0	20.0	31.3
50.0	40.0	62.5
75.0	60.0	93.8
88.0	70.4	110.0
100.0	80.0	125.0
112.0	89.6	140.0
125.0	100.0	156.3
137.0	109.6	171.3
150.0	120.0	187.5
175.0	140.0	218.8
200.0	160.0	250.0
300.0	240.0	375.0



This potential variance in the effective dosage which is attributable to acceptable bioequivalence ranges is unknown (since direct comparative T_4 bioequivalence studies are not required) and not disclosed to the practitioner. The adverse effects of this variance are borne by the patient who might be prescribed for example a 100 mcg dose of T_4 and actually receive a range of doses from 80 mcg to 125 mcg, encompassing as many as 4 labeled dose levels. This variance with the attendant changes in serum TSH levels can lead to chemical hyperthyroidism and the risk of atrial fibrillation or hypothyroidism and unwanted symptoms, altered lipid levels or cardiac contractility and accelerated atherosclerosis.[4,21,27] As a result, the patients may well require repeated dose adjustments to restore TSH to normal if the drug preparation (brand) is changed.

In addition to this drug product related variability, patient-to-patient variability in L-thyroxine dosing results from variations in gastrointestinal absorption. Gastrointestinal absorption can be altered by the dissolution properties of the pharmacologic preparation, individual changes in gastric and small intestinal pH, transit time through the GI tract, primary GI pathology including sprue and celiac disease, the residual effects of hypothyroidism on GI function and lastly the presence of interfering substances such as a variety of food stuffs, minerals and medications which may alter drug absorption.[28]

At the present time there are seven FDA approved formulations of L-thyroxine. They are Levoxyl®, Synthroid®, Levo-T®, Thyro-Tabs®, Novothyrox®, Unithroid® and Mylan's® generic product rated by FDA equivalent to Unithroid. Three of these, Levoxyl®, Synthroid®, and Unithroid®, are readily available for the treatment of patients. Each is manufactured in twelve tablet strengths from 25 to 300 mcg and is designed to be taken once a day on an empty stomach. Physicians and pharmacists have observed that the recently approved T_4 formulations have differences in their physical dissolution properties. One formulation dissolves on exposure to even the slightest amount of moisture, beginning dissolution in the oral-pharynx on exposure to saliva. It can be predicted that the rate of drug absorption for each of the new branded preparations is directly related to the dissolution (rate and extent) of the formulation. A formulation with more rapid and complete dissolution would result in increased drug delivery efficiency and also in more rapid and uniform oral absorption.

Studies of these formulations in normal human volunteers are complicated and potentially not relevant to the hypothyroid patient population since the same mechanism of increased drug availability would lead to a fall in serum TSH blunting the endogenous thyroid gland production of T_4.[2] This variation in endogenous thyroid gland function would be expected to obscure differences between T_4 replacements as reflected by observed PK parameters including T_{max}, C_{max}, and area under the curve (AUC). It could be predicted that peak concentration and time to peak concentration would be improved in formulations with more rapid and complete dissolution when compared to formulations that are less efficient in dissolution. These differences may be further enhanced when observed in patients with comorbid conditions and in real life environments compared to normal volunteers under controlled investigational environments.

The non-equivalence of these differing pharmacologic preparations resulting from the difference in tablet dissolution may not be reflected in studies using supra pharmacologic

dosing. In studies performed by Carr, *et al.*[22] it was shown that changes in daily L-thyroxine dose of as little as 25 mcg led to significant changes in TSH. These changes in TSH in turn reflected the fact that patients previously well maintained with thyroid hormone replacement were then rendered either chemically hypothyroid or hyperthyroid.

Using a test dose of 600 mcg (300 mcg x 2) could easily miss such important differences and thus give the false impression that two differing preparations were similar when in fact they were not.

7. INTERFERENCE WITH L-THYROXINE ABSORPTION

It has been well established that a variety of foods including soy, minerals such as calcium and iron, and drugs such as cholestyramine and sucralfate, can have marked effects on L-thyroxine absorption.[14] These changes can be especially significant during pregnancy when the L-thyroxine treatment dosage typically increases.[29] Labeled recommendations advise that patients refrain from eating for up to one hour after receiving oral L-thyroxine. Differences in absorption that result from interference with food is likely to relate to changes in dissolution. A reasonable hypothesis that deserves clinical investigation is that interference in dissolution from food and other orally consumed substances would be significantly less leading to a greater degree of bioavailability in formulations that have a more rapid dissolution. These differences would not be expected to manifest themselves when compared to a "standard" L-thyroxine dose given in liquid form as currently recommended by FDA guidelines.[26]

8. BIOEQUIVALENCE OF L-THYROXINE PREPARATIONS IN STUDIES PERFORMED IN HYPOTHYROID PATIENTS

Currently comparative bioavailability studies are performed in euthyroid human volunteers. While this may be sufficient to assess certain aspects of GI absorption there are additional considerations which need to be addressed to provide clinicians important dosing comparisons before treating target populations, specifically patients with hypothyroidism. As a result of hypothyroidism there is a decrease in gastric acid production, decreased GI motility, increased edema of the bowel wall, and as a result of overlapping autoimmune diathesis, an increased prevalence of sprue and other autoimmune small bowel disease.[30] Therefore, it is neither possible nor appropriate to assume that dissolution and absorption of the L-thyroxine preparation in the stomach or its absorption throughout the GI tract will be equivalent in hypothyroid patients to that of normal volunteers. Thus the relevant equivalent studies need to be performed in patients with an established diagnosis of hypothyroidism while being maintained on a steady state dose of medication.[26] Indeed, in hypothyroid patients in whom there is no endogenous T_4 or T_3 production by the thyroid gland and in whom simultaneous regulation of TSH by exogenous thyroid hormone is not a relevant variable, the results of bioavailability testing measuring the serum concentration, time to peak concentration and the AUC provide the desired degree of relevance with regard to bioavailability. It is only in these patients that the variety of relevant clinical measures including serum cholesterol, resting heart rate, red cell sodium potassium ATPase, and the

variety of cardiovascular hemodynamic parameters under thyroid hormone regulation can be properly assessed.[7,13] As emphasized above, these measurements need to include TSH assayed during steady state T_4 replacement.[20]

9. CONCLUSION

The treatment of hypothyroidism with standardized preparations of L-thyroxine is well established. At the present time there are three widely used FDA approved formulations of L-thyroxine. Physicians and pharmacists have observed that the newly FDA approved T_4 formulations have different dissolution properties. As a result of changes in the new T_4 formulations it will be necessary to prove that bioavailability and equally important clinical efficacy of these preparations are in fact equivalent. Variations in dosing by as little as 15%-20% (within guidelines) can produce substantially greater changes in TSH levels and place patients at risk for subclinical hypo- or hyperthyroidism; the latter condition placing patients at increased risk for atrial fibrillation. It can be assumed from a variety of relevant clinical parameters (e.g., patient-specific gastrointestinal absorption, *in vivo* hormone metabolism involving the conversion of T_4 to T_3, and possible food effect differences) that in fact these preparations are not similar and should therefore not be considered appropriate equivalents.

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