



Levothyroxine Sodium – An Overview of Challenges Related to Interchangeability and Stability of Different Formulations



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Abstract

Since the early 1950s, oral levothyroxine sodium (L-T4) has been the primary form of treatment for hypothyroidism. There are currently several brands and generic options available to patients, some of which are considered bioequivalent. In the last two decades, however, several reports have shown loss of therapeutic control in patients after switching to a different, albeit bioequivalent, L-T4 product. Such observations can partly be explained by L-T4's narrow therapeutic index, which means small changes in the dose can lead to therapeutic failure or adverse events. Thyroxine (T4) is also a labile compound and several products have been recalled due to stability or potency issues. These recalls have led regulatory agencies, such as the FDA, to revise the methods used to determine bioequivalence. Notwithstanding, several professional organizations have suggested that the current methods of determining bioequivalence are inadequate for establishing the therapeutic equivalence of levothyroxine sodium products. In addition to bioequivalence concerns, L-T4 tablets have been subject to several recalls due to stability and potency issues. This article examines how formulation properties, excipients, and tablet handling practices can influence the stability of L-T4 tablets. In addition, it provides a summary of L-T4 interchangeability in North America and provides an overview of L-T4 tablets recalls due to sub potency. Finally, it explores some of the challenges with the current method of establishing bioequivalence and discusses some of the risks associated with unintended dose changes of levothyroxine sodium.

Keywords: Thyroid; Bioequivalence; Hormone; Formulation

Introduction

Hypothyroidism is a common endocrine disorder affecting 2-5 % of the general population [1,2]. Oral levothyroxine sodium (L-T4), the mainstay of replacement therapy, is currently available under various brand names and generic versions [3]. Regulators, such as the United States Food and Drug Administration (FDA) and Health Canada, are responsible for determining the bioequivalence of the various L-T4 preparations marketed in their jurisdiction. In the US, several L-T4 preparations are considered bioequivalent, thus allowing patients to hypothetically switch between products without experiencing adverse drug reactions or therapeutic failure. However, there are well documented cases of either therapeutic failure or adverse events occurring when switching from one bioequivalent product to another [4,5]. This led the American Thyroid Association (ATA) and American Association of Clinical Endocrinologists (AACE) to classify L-T4 as a narrow therapeutic index or critical dose drug capable of causing significant adverse outcomes including dyslipidemia, poor pregnancy and fetal outcomes, atrial fibrillation, bone loss, and exacerbation of heart disease from small dose changes [6,7].

Over the last two decades, the FDA has made several changes in the regulatory requirements for marketing L-T4 tablets. In 1997, after several cases of adverse events being reported as a result of switching between brands and differences related to stability and potency of different preparations, the FDA declared L-T4 as a new drug; therefore, all L-T4 manufacturers in the US had to submit a new drug application (NDA) and in the process, establish bioequivalence with an approved reference product [8]. L-T4 products which did not satisfy the stability requirements of the FDA were discontinued. Subsequently, after numerous drugs recalls due to sub-potency, the FDA further tightened the stability requirements of L-T4 tablets in 2007 and the potency requirement during normal shelf-life was increased from 90 % - 110 % to 95 % -105 % [9]. Despite these measures, reports of loss of therapeutic efficacy and adverse events continue to occur in patients switching between brands or generics.

L-T4 requires a strict and consistent dosing regimen to achieve therapeutic effects. In addition to drug potency, drug

and food interactions, drug-drug interactions, comorbidities, and poor compliance affect bioavailability and consequently lead to variability in the efficacy of L-T4. For instance, Hashimoto's thyroiditis, which is the commonest cause of hypothyroidism in North America, is associated with a higher incidence of immune-mediated inflammatory gastrointestinal conditions, which can affect L-T4 absorption. While a detailed discussion of the underlying mechanism is outside the scope of this article, many commonly used foods, drugs and supplements can interfere with L-T4 absorption. Certain drugs and supplements like bile acid sequestrants, calcium carbonate, and iron supplements tend to form stable and insoluble complexes with L-T4 interfering with its absorption [10-12]. On the other hand, drugs such as proton pump inhibitors and cholestyramine also inhibit L-T4 absorption by altering the gastrointestinal (GI) motility and pH [13-15].

Therefore, patients are advised against taking supplements or medications at least one hour after taking their L-T4 dose [16]. It is also recommended that L-T4 be taken on an empty stomach, because many food products including coffee can affect bioavailability [16]. Given these considerations and the narrow therapeutic index of L-T4, it is recommended that patients take L-T4 at the same time either each morning or at bedtime to ensure the consistency of each dose. Other regimens such as taking a slightly larger dose of L-T4 2-3 times a week instead of a daily dose have also been recommended to improve absorption [17]. While other reviews have addressed some of the issues regarding L-T4 stability, methods of establishing bioavailability and challenges associated with switching between L-T4 products this paper highlights the often-neglected effects of physicochemical properties of L-T4, excipients and tablet handling practices that affect stability and efficacy causing loss of therapeutic control [18-22].

Methods

A comprehensive literature search was conducted in Embase and Medline (via Pubmed) using a combination of the following keywords: levothyroxine AND interchangeability OR bioequivalence AND stability OR potency. The literature search was conducted between December 2019 and September 2020 and it included articles published from 1997, the year the FDA

updated its regulation on levothyroxine, to 2020. No conference proceeding or presentation was included.

Discussion

The Interchangeability of L-T4 Products in Canada and the US

Prior to 1962, the FDA did not require drug manufacturers to prove the efficacy of their products. As long as the product was safe, it could be sold to the public. However, following the 1962 Kefauver-Harris Drug Amendments, manufacturers were required to prove both safety and efficacy of their products [23]. Consequently, the FDA conducted a review of all the drugs that had been approved between 1938 and 1962. This evaluation was conducted under the Drug Efficacy Study Implementation (DESI) program. Since L-T4 had been available in the US prior to 1938, it was exempted from the FDA evaluation. In 1997, however, the FDA declared L-T4 as a new drug mandating the submission of a New Drug Application (NDA). This process was integral to the regulation of the number of L-T4 products currently available in Canada and the US. Currently, two brands of L-T4 are being sold in Canada: Synthroid (BGP Pharma ULC) and Eltroxin (Aspen Pharmacare Canada Inc.). These brands have been in the market since the 1950s. They are not interchangeable and do not have any generic equivalents available for human use [24].

In the US, there are nine L-T4 manufacturers: seven brands and two generics. The section of the FDA Orange Book (which lists the therapeutic equivalence of drugs in the US) concerned with L-T4 bioequivalence is summarized in Table 1. The FDA currently has four reference standards for establishing L-T4 bioequivalence. Each reference (i.e., Unithroid, Synthroid, Levoxyl, and Levothyroxine sodium) has a corresponding bioequivalence or AB code (Table 1). A product that shows bioequivalence with a reference shares the same AB code. L-T4 manufacturers can choose to establish bioequivalence with any or all the reference standards. For example, AB3 is the code for the third reference standard drug, Levoxyl. Manufacturers wishing to obtain AB3 status will have to compare their product with Levoxyl. Currently, only Levo-T, Unithroid, and Levothyroxine have AB3 status. Therefore, patients on Levoxyl should, in theory, experience a similar therapeutic effect with Unithroid, Levo-T, or Levothyroxine.

Table 1: FDA bioequivalence classification of L-T4 products.

Equivalence Code (Reference Drug)	AB1 (Unithroid)	AB2 (Synthroid)	AB3 (Levoxyl)	AB4 (Levothyroxine Sodium)
Synthroid (Abbvie)	+	+		
Levo-T (Cediprol Inc.)	+	+	+	
Unithroid (Stevens J)	+	+	+	
Levothyroxine Sodium (Mylan)	+	+	+	+
Levoxyl (King Pharm)	+		+	

Stability of Oral L-T4

L-T4 is one of the most recalled drugs in the US. From February 2012 to December 2018, nineteen recalls due to sub potency, and super potency of L-T4 tablets occurred in the US as summarized in Table 2. The most common reason for these recalls was sub-potency during the shelf life of the drug. The expiry date of a drug is usually determined from the results obtained from stability testing in which the drug potency will remain between 95-105% [25]. A 10% reduction for most drugs may not pose any health

risk, but because L-T4 is a narrow therapeutic index drug, such a decrease in dose could result in lowering of the therapeutic effect. For example, the next lowest dose for a patient on Synthroid 150 µg is the 137 µg tablet and if 10% of the 150 µg tablet degrades, the effective dose would be 135ug, which would be less than the next available lower dose [26]. Before the 2007 regulatory changes in potency requirements, the FDA obtained results of stability studies of all oral L-T4 products available in the US from 2003-2005 [13].

Table 2: FDA recalls due to super potency or sub potency of L-T4 products in the US from February 2012 to December 2018.

Recall Initiation Date	Product Description	Recalling Firm	Product Quantity	Reason for Recall
2/24/2012	Levothroid	Lloyd Inc.	19,039 bottles	Subpotent Drug
2/3/2012	Levothroid	Lloyd Inc.	19,166 bottles	Subpotent Drug
7/25/2012	Levothroid	Lloyd Inc. of Iowa	37,441/100-tablet bottles	Subpotent Drug
10/29/2012	Levothyroxine Sodium	Alara Pharmaceutical Co	7,432 bottles	Subpotent Drug
11/15/2012	Levothyroxine Tablets	Physicians Total Care, Inc.	90 pills	Subpotent Drug
4/30/2013	Levoxyl	King Legacy	33,227 bottles	Subpotent Drug
4/30/2013	Levoxyl	King Legacy	51,591 bottles	Subpotent Drug
4/30/2013	Levoxyl	King Legacy	112,914 bottles	Subpotent Drug
4/30/2013	Levoxyl	King Legacy	77,272 bottles	Subpotent Drug
4/30/2013	Levoxyl	King Legacy	103,796 bottles	Subpotent Drug
4/30/2013	Levoxyl	King Legacy	51,438 bottles	Subpotent Drug
4/30/2013	Levoxyl	King Legacy	107,236 bottles	Subpotent Drug
4/30/2013	Levoxyl	King Legacy	195,699 bottles	Subpotent Drug
4/30/2013	Levoxyl	King Legacy	194,142 bottles	Subpotent Drug
4/30/2013	Levoxyl	King Legacy	195,201 bottles	Subpotent Drug
1/14/2014	Levothyroxine Sodium	Mylan Pharmaceuticals Inc.	138,970 bottles	Subpotent Drug
9/12/2016	Levothyroxine Sodium	Moore's Compounding Pharmacy	90 capsules	Superpotent Drug
11/7/2016	Levoxyl	Pfizer Inc.	2,666 bottles	Superpotent Drug
12/6/2018	Levoxyl	Pfizer Inc.	1996 bottles	Superpotent Drug

The stability data showed that some L-T4 products degraded significantly before the expiration date which led FDA to impose a more stringent potency requirement of 95-105% over the shelf life. The cause of this loss of stability, despite controlling for the known destabilizing factors like heat, light, humidity, oxidation and pH, remains unclear [27]. Consequently, instead of improving the stability of L-T4, the new potency requirement may have led to a reduction in the shelf-life of L-T4. Several explanations for the loss of stability have been suggested. Patel et al. suggested that it might have been due to formulation excipients and formulation pH and recommend the use of non-hygroscopic excipients and basic pH modifiers [28]. They also showed that high moisture content and low pH are closely associated with L-T4 degradation. Another study proposed that L-T4 stability is dependent on the impact of

oxygen and moisture and suggested that the loss of the bound hydrates in L-T4 is responsible for the observed instability [29].

They surmised that the stability of L-T4 is compromised after dehydration by the presence of oxygen and that L-T4 is more stable in moist conditions with high relative humidity than in dry conditions and recommended against the use of hygroscopic excipients which disrupt the bound water molecules in L-T4. Similarly, a study using the solid-state characterization found that L-T4 loses its hydrates at relative humidity of less than 45% and showed that L-T4 is susceptible to degradation by high temperatures, low humidity, and oxygen [30]. Together, these findings suggest that L-T4 is unstable in low humidity but stable in high humidity as long as its water molecules are maintained.

Tablet Properties

To determine bioequivalence, the FDA adapted The Biopharmaceutics Classification System (BCS), which is used to predict drug bioavailability based on the solubility and permeation of the drug. Thus, rather than testing bioequivalence of certain batches, disintegration, dissolution, and friability test are done, and bioequivalence and potency can be estimated based on the BCS designation of the drug. Since L-T4 has a highly variable individual absorption it is often classified as a Class III drug (high solubility and low permeability) [31]. Rate and extent of dissolution are factors considered to be critical for the absorption of a solid oral dosage form. To maintain consistency among oral preparations, it is important that they share similar dissolution profiles to ensure rapid and complete absorption. Minor differences in dissolution rates have been observed between L-T4 preparations, which may contribute to some of the observed variations in absorption.

Although, it is suggested that small discrepancies in dissolution rates are clinically irrelevant to most patients, the dependence on this property in determining bioequivalence and the potential variability in the gut, especially hypothyroid patients with absorption disorders exploration remains unclear. This was borne out in a study by Pabla et al. showing significant difference in the rate of dissolution with changes in pH between L-T4 products otherwise considered bioequivalent [32]. They reported that the

dissolution of three different products decreased with an increase in pH, and the variation in the rate of dissolution was significantly higher between pH=2 and pH=5. Patients with altered gastric acid production, such as those on proton pump inhibitors or with diseases such as chronic gastritis, could experience less drug dissolution, especially considering the low pH of the stomach [33-35]. L-T4 absorption primarily occurs in the distal jejunum and ileum and drug dissolution occurs primarily because of the pH in those regions. Similarly, patients with autoimmune inflammatory bowel disorders, which are associated with Hashimoto's thyroiditis are susceptible to variability in dissolution rates because of the alteration in the pH of the GI system [36].

L-T4 is an amphoteric molecule with three pKa values: 2.2 (COOH), 6.7 (OH), and 10.1 (NH₂). Drug solubility is high below pH 2.2 and above 10.1, with its lowest solubility between pH 4 and 5 [37,38]. As a result, L-T4 dissolution is highest in the stomach, where the pH is very low [33]. The various effects of pH on the dissolution rates of different L-T4 formulations are further complicated due to differences in the drug particle sizes, excipients, and manufacturing processes of each product which can also affect dissolution. In most L-T4 formulations, excipients constitute the bulk of the drug; the amount of L-T4 in a tablet can be as small as 25 µg, so the excipient to drug ratio is usually high. Table 3 shows five current L-T4 brands and the different excipients which are usually present in the different products.

Table 3: Common excipients used in preparation of L-T4 tablets.

Tablets Excipients	Synthroid	Levo-T	Levothyroxine Sodium	Levoxyl	Unithroid
Binders and Diluents					
Acacia	+				+
Lactose monohydrate	+				+
Providone	+		+		
Cosopovidone					
Microcrystalline Cellulose		+	+	+	+
Mannitol			+		
Sucrose			+		
Confectionary Sugar	+				
Talc	+				
Crospovidone			+		
Calcium Sulfate Dihydrate				+	
Corn Starch					+
Lubricant					
Magnesium Stearate	+	+	+	+	+
Disintegrant					
Croscarmellose Sodium				+	
Colloidal Silicon Dioxide		+	+		
Sodium Starch Glycolate	+				+
Antioxidant					
Butylated Hydroxyanisole			+		

Surfactant					
Sodium Laurel Sulfate			+		
Preservative					
Ethyl Alcohol			+		
Buffering Agent					
Sodium Bicarbonate				+	

Effects of Excipients on Stability

Excipients are integral components of oral therapies. They can affect drug dissolution, stability, and other factors that may affect bioequivalence. The effects of excipients are significant in L-T4 because of its small dose concentration in the tablet. One of the most apparent differences between L-T4 brands is the excipients present in their formulations. Although excipients are often physiologically inactive, their physicochemical properties can affect drug stability. The FDA data on L-T4 recalls showed that some brands had more recalls than others due to sub potency [25].

One study looked at the effects of humidity and heat on the degradation and analyzed how different excipients can affect L-T4 degradation [39] and showed that significant degradation of L-T4 occurred at high temperature and humidity, especially in the presence of crospovidone, povidone, and sodium lauryl sulfate. Povidone and crospovidone showed significant hygroscopicity (>10% water gain), making moisture the likely degrading agent. Sodium lauryl sulfate, another common excipient in L-T4 tablet formulations showed deliquescent activity in the presence of moisture, which is significant, as this will also affect tablet hardness as well as promote drug degradation. These specific excipients are present in several, but not all, of the available L-T4 formulations. Brands containing such excipients are susceptible degradation, especially if the drug products are not correctly stored. Another study showed similar effects of crospovidone and povidone on the stability of L-T4 and also showed that L-T4 degrades much faster at lower pH than it does at higher pH and reported that pH modifiers, including sodium bicarbonate, reduced L-T4 degradation [28].

Tablet Splitting

Given the wide range of L-T4 dosages, tablet splitting is not generally required. However, patients may decide to split their L-T4 tablets to save costs or reduce the drug into ingestible pieces. The latter mostly occurs when administering tablets to children or individuals swallowing difficulties. Tablets can either be split manually or mechanically; however, studies have shown an uneven distribution of active compounds between the two halves, as well as significant loss of the tablet, which is fractured off during the splitting process. Some studies have questioned the validity and safety of this process, especially with narrow therapeutic index drugs such as L-T4 showing heterogeneous distribution of the

active compound, depending on the manufacturing process and tablet binder used [40]. Tablet splitting also leads to the increased surface area to volume ratio and disruption of the external coating. As a result, splitting a tablet might accelerate the effects of hygroscopic water adsorption, fragmentation, friability, and degradation of L-T4. Thus, if degradation is increased by tablet splitting, the differences in the stability of the divided tablet may also be affected.

Implications of Unintended Dose Changes in a Narrow Therapeutic Index Drug

A narrow therapeutic index drug is defined as any drug that has a less than 2-fold difference between the minimum toxic concentration and minimum effective concentration [41]. Drugs like warfarin, tacrolimus, phenytoin, carbamazepine, and L-T4 are examples of narrow therapeutic index drugs. Small unintended changes in L-T4 doses can lead to significant clinical effects [42]. Although overt symptoms related to grossly abnormal thyroid hormone levels may occur due to unintended dose changes, more subtle subclinical changes are not uncommon. which may account for approximately 90% of the observed adverse events in patients [4]. The study also reported that switching from brand products to generic formulations was associated with a higher incidence of adverse events which included development of new symptom or loss of therapeutic control of TSH levels and found that in over 90% cases switching to a different L-T4 product was done either by the pharmacy or patient without the clinician’s knowledge [4]. These findings emphasize importance of consistent dosing in the treatment of hypothyroidism. The prevalence of subclinical hypothyroidism is estimated between 14-21% in patients treated with L-T4 [4]. A meta-analysis involving 55,287 hypothyroid patients (3450 with subclinical hypothyroidism) showed a significant increase in the risk of coronary heart disease (CHD) and cardiovascular mortality in patients with subclinical hypothyroidism compared to euthyroid patients [43]. These risks were independent of age, gender, or preexisting cardiovascular conditions. These findings were supported by another meta-analysis that involve 14,449 patients [44]. Other studies have also shown an association between subclinical hypothyroidism and increased risks in left ventricular systolic and diastolic dysfunction, increased systolic time interval, elevated total cholesterol, low density lipoprotein cholesterol (LDL-C) and triglyceride levels, and homocysteinemia [45-47].

Reliance on Pharmacokinetic Parameters for Bioequivalence

Bioequivalence of L-T4 is typically assessed by administering the reference drug and potential equivalent to healthy, euthyroid individuals. Serum or plasma samples are then taken at regular time intervals to determine pharmacokinetic (PK) parameters such as time taken to reach maximum concentration (T_{max}), area-under-the-curve (AUC), and peak concentration (C_{max}). Currently, plasma C_{max} and AUC of thyroid hormone (T₄) are required to be within 80-125% of each other when the two L-T4 products are given to healthy euthyroid individuals [25]. L-T4, however, is a synthetic variant of the endogenous T₄ which is metabolized to its active metabolite triiodothyronine (T₃) within the cells thus making it difficult to measure intracellular T₃ levels. To reduce the effect of endogenous T₄, the FDA Guidance for Industry stipulates that bioequivalence studies are to be done using pharmacological L-T4 dose of 600 µg. The FDA also recommends pre-dose baseline correction to account for endogenous T₄ levels [19].

Despite these measures it is suggested that the current equivalence methods are inadequate for determining L-T4 bioequivalence [7]. Consequently, some experts suggest the addition of a pharmacodynamics approach to bioequivalence studies. The rationale being that since L-T4 is administered in euthyroid patients, TSH levels are suppressed as T₄ levels increase; as a result, bioequivalent drugs will show not only comparable PK results but also show similar TSH levels [48]. While some have supported the advantages of using TSH as a pharmacodynamics marker in bioequivalence analysis [26], it is noteworthy that there may be a test-to-test variability in TSH making it hard to compare different results. Another contentious issue is the use of healthy euthyroid individuals to determine bioequivalence. Since endogenous T₄ cannot yet be effectively distinguished from exogenous L-T4, healthy individuals with functioning pituitary-thyroid feedback system will down-regulate TSH production, resulting in less plasma T₄ which has led some to suggest that thyroidectomized patients are the ideal group for establishing bioequivalence [26]. Since thyroidectomized patients cannot endogenously produce thyroid hormones, baseline T₄ will strictly be dependent on the administered L-T4 dose. Furthermore, lower, and safer doses of L-T4 will be required for bioequivalence studies if treated thyroidectomized patients are used instead of healthy individuals [26]. A study showed that dosages varying as much as 12.5% with baseline correction and 35% without correction for baseline could pass equivalence studies [26]. Such findings emphasize the need for a revision of the current method, especially when the differences in marketed tablet strengths are usually between 25-33%.

Conclusion

Patients should, ideally, be able to substitute drug products with bioequivalent products without concern of adverse events

or therapeutic failure. However, the labile nature of L-T4 requires strict monitoring when switching between brands or from brands to generic formulation. Since excipients constitute a significant portion of L-T4 tablets, their effect on the stability either through pH or moisture regulation should be carefully considered by manufacturers of L-T4. The recent studies on L-T4 stability shows the importance of maintaining its waters of hydration and proper understanding of its solid-state characteristics. L-T4 is not only a narrow therapeutic index drug, but a peculiar drug which is more stable in the high relative humidity, than in low relative humidity. Therefore, storage conditions of L-T4 should appropriately reflect these unique characteristics and also guide manufacturers in improving formulation practices. Finally, regulatory agencies such as the FDA should consider the benefits of including the assessment of pharmacodynamics parameters in establishing bioequivalence.

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