Review Article

Levothyroxine Replacement Therapy: A Focus on Synthroid

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ABSTRACT

Hypothyroidism is one of the most common endocrine disorders, affecting nearly 5% of the American population. Prior to the 1890s, there was no available treatment for hypothyroidism. The earliest treatments involved administering either powdered desiccated thyroid glands from animals or liquid thyroid extract. Innovation and regulation have significantly improved the quality of treatment for hypothyroid patients. Currently, the mainstay of treatment is oral levothyroxine sodium tablet replacement therapy. Although thyroid management is fairly straightforward, levothyroxine stability and product interchangeability have been recurring issues. This article reviews (1) the historical significance levothyroxine has had since its inception, (2) the effects of regulation on formulation and sale of levothyroxine, (3) protocol required for establishing bioequivalence using Synthroid, and (4) some policy considerations and recommendations concerning bioequivalence and interchangeability of levothyroxine.

Keywords: Levothyroxine, bioequivalence, interchangeability, potency, regulation.

INTRODUCTION

Hypothyroidism is a common endocrine disorder that is characterized by low amounts production of thyroid hormones by the thyroid gland. It is estimated that about 4.6 % of American adults are hypothyroid[1]. One of the most common causes of hypothyroidism is Hashimoto's autoimmune disorder, which occurs when the immune system attacks the thyroid gland of an individual. Surgical removal and radiation therapies are some other events that can disrupt thyroid production. The thyroid gland produces two major hormones, thyroxine (T4) and triiodothyronine (T3). T3 is the physiologically active hormone and T4 is converted to T3 in the peripheral cells. Low T4 can lead to several metabolic and developmental dysfunctions in humans. Hypothyroid patients require regular thyroid hormone replacement from exogenous sources. The mainstay of thyroid treatment is oral levothyroxine sodium tablet. Currently, there are six U.S. Food and Drug Administration (FDA) approved levothyroxine tablet products available in the market: Levo-T, Levothyroxine Sodium, Levoxyl, Novothyrox, Synthroid, and Unithroid. Synthroid, however, is the most popular thyroxine brands in North America based on prescription patterns[2]. The two major issues facing levothyroxine tablets are stability and interchangeability (or bioequivalence). Most of the focus on levothyroxine instability has been on the effects of excipients. Several studies have identified incompatible compounds that either expedite or facilitate the degradation of levothyroxine[3,4]. According to the FDA, Synthroid is classified as an AB2 reference drug and is therefore bioequivalent to Levo-T, Unithroid, and Levothyroxine Sodium. Studies, however, show that patients experience adverse events or inadequate therapeutic control when patients switch between brands or from brand to generic[5-7]. The dominant explanation for the lack of bioequivalence, even between theoretically equivalent brands, is that levothyroxine is a narrow therapeutic index (NTI) drug and, as such, very small changes in the dose can affect the safety and efficacy of the drug. Synthroid, however, has benefitted from the NTI designation of levothyroxine. In addition to extensive marketing of the drug and support from various thyroid associations (American Thyroid Association, The Endocrine Society, the American Association of Clinical Endocrinologists etc.), the manufacturers of Synthroid have been able to convince health professionals and patients that switching between levothyroxine preparations is not safe. This review will briefly discuss the history of levothyroxine. It will also examine how FDA policies have impacted the formulation of levothyroxine products and the protocols required for establishing bioequivalence using Synthroid as reference. Finally, it will address some policy considerations and recommendations concerning bioequivalence and interchangeability of levothyroxine.

Method

The approval package of Synthroid was accessed through the FDA website. The "Search Drugs@FDA" section on the homepage served as the entry point to the drug information database. The drug name Synthroid was inputted to obtain the approval history and other approval documents. The important documents examined for the purpose of this review were the approval letter, memos or correspondence, and medical reviews. A general literature search on PubMed with the terms: "Levothyroxine sodium + Synthroid + FDA" (between years 1950 and 2001)

provided sufficient published materials on thyroid replacement therapies within that time period. Only documents with specific references to Synthroid were selected for the purpose of this study.

Historical Perspective on the Development of Thyroid Treatment

The use of replacement therapy for the treatment of hypothyroidism dates back to the late 1800s. Before the discovery of thyroid replacement, physicians transplanted the thyroid gland of sheep and pigs to patients in order to treat hypothyroidism [8]. In 1891, two Portuguese research collaborators Bettencourt and Serrano discovered that rather than the thyroid organ, "thyroid juice" was responsible for the benefits observed after transplantation [9]. Bettencourt and Serrano had observed that some of the benefits of thyroid transplantation occurred almost immediately after the transplant. Considering that the body required a significant amount to time to establish the necessary vasculature with the transplanted organ, they hypothesized that the secretion of the thyroid might be responsible for the benefits of thyroid transplantation [9]. Only three months after Bettencourt and Serrano had proposed the "thyroid juice" hypothesis, an English physician, George Murray reported the successful treatment of a patient with myxedema coma, a severe form of hypothyroidism with thyroid secretion. Murray subcutaneously injected sheep thyroid extract to a 46-year-old woman who had been diagnosed with myxedema coma [10]. After Murray's report, other physicians reported successful treatment of myxedema coma through oral administration of thyroid extracts from pigs [11]. Although the isolation of thyroxine, which is the active compound in the extract, was achieved in 1915 by Edward Kendall, an American chemist, commercial sales did not begin until 1949 [8, 12]. Since 1949, oral thyroxine replacement therapy has been the primary method for the treatment of hypothyroidism. In 1997, after nearly 50 years of being a prescription therapy, the FDA reclassified products containing levothyroxine sodium, the synthetic version of thyroxine, as new drugs. This announcement was prompted by the large number of recalls of products containing levothyroxine sodium that occurred between 1990 and 1997.

Notable Policy Milestones

The 1906 Federal Food and Drug Act prohibited the sale of mislabeled or adulterated drugs [13]. This statute did not, however, require drugs to be approved by the FDA. Manufacturers could, therefore, sell their products without pre-market approval provided the physicochemical characteristics of the drugs matched the United States Pharmacopeia and National Formulary, and the label listed all the constituents of the drug [14]. The 1938 Federal Food, Drug, and Cosmetic (FDC) Act required manufacturers of new drugs to prove drug safety before marketing. Drugs which were already on the market before this date were exempted from this statute [14, 15]. The 1962 Kefauver-Harris Drug Amendments required manufacturers to not only prove the safety but also the efficacy of their drugs [14]. During this period, the FDA also conducted a review of all the drugs that had been approved between 1938 and 1962 [15]. This evaluation was conducted under the Drug Efficacy Study Implementation (DESI) program. Levothyroxine sodium products were able to avoid FDA evaluation because thyroxine, which is the natural equivalent of levothyroxine sodium, was used in the treatment of hypothyroidism prior to 1938. The statue, therefore, grandfathered levothyroxine sodium, exempting its products from FDA evaluation. August 14th, 1997, the FDA publicly declared that oral therapies containing levothyroxine sodium were new drugs. According to the Centre for Drug Evaluation and Research (CDER), a drug is "a 'new drug' (which will require a product specific application to be approved by FDA) if it is not generally recognized among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the condition prescribed, recommended, or suggested in the labeling" [15]. The primary reason provided by the FDA for this announcement was the numerous recalls that occurred between 1990 and 1997. It is estimated that 100 million tablets from 150 lots were recalled during that period [16]. The reason for these recalls included sub-potency, super-potency, and stability issues. Because levothyroxine products did not require FDA approval, manufacturers would often change the formulation of their product either to improve stability or potency [17]. In addition, levothyroxine is a labile compound, susceptible to degradation by heat, light, and humidity [18]. These factors, therefore, required strict oversight on the manufacturing procedures of the companies involved in the production of this drug. The FDA directed manufacturers who wanted to continue to sell levothyroxine products to either submit a new drug application (NDA) or file a citizen petition to obtain an NDA exemption. While the deadline to file a citizen petition was October 14, 1997, two months from the date of the announcement, manufacturers had three years (August 2000) to submit an NDA (the NDA deadline was later extended to August 2001) [18]. Since there was no alternative drug for hypothyroid patients, the FDA allowed manufacturers to continue to sell levothyroxine products during the approval period.

Synthroid

In response to the 1997 Federal Register Notice, Knoll Pharmaceutical Company, the manufacturers of Synthroid at the time, decided to file a citizen petition. Knoll claimed that levothyroxine was considered safe by the experts because it was frequently prescribed for the treatment of hypothyroidism[19]. Furthermore, Knoll cited several scientific studies which proved the safety and effectiveness of Synthroid. Knoll also highlighted several long-term contracts to supply significant amounts of Synthroid to the US Veterans Administration and Public Health Service [20]. They suggested that the FDA's decision to classify levothyroxine sodium (i.e. Synthroid) as a new

drug was illogical because the FDA approved most of the government contracts for Synthroid supply. Knoll also insinuated that the FDA was using the incompetence of other manufacturers to "seek additional and unwarranted authority to regulate Synthroid" [19, 20]. Abbott Laboratories acquired Knoll Pharmaceuticals on March 2nd, 2001 [18]. The reason for the acquisition is unclear, but, shortly after, Abbott dropped the citizen petition and submitted an NDA for Synthroid; the NDA was submitted on July 31st, 2001 (NDA 21 – 402) [18]. The FDA evaluated the application submitted by Abbott and approved Synthroid on July 24th, 2002. Abbott Laboratories was expected to complete two post-market requirements [18]:

1. Develop an appropriate analytical method for the estimation and identification of impurities and degradants.
2. Submit chemistry, manufacturing, and controls protocols required for the production Synthroid.

The FDA required an annual update on the progress of these commitments.

Abbott submitted two main studies (Table 1): M01-324 which assessed bioavailability and safety, and M01-323 which assessed bioequivalence and safety. M01-324 was an open-label, single-dose randomized, 2-way crossover study which compared two 300 µg Synthroid tablets to 600 µg of levothyroxine solution: 32 healthy individuals (16 males and 16 females) aged 18-50 years old participated in the study (three participants did not complete the study) [19]. No life-threatening adverse event was observed in the study. M01-323 was an open-label, single-dose, randomized, three-period, six-sequence, cross-over study design which determined the bioequivalence of three Synthroid strengths: 50 µg, 100 µg, and 200 µg (each administered as 600 µg dose): 36 healthy adults (18 males and 18 females) aged 18 - 50 years old participated in the study (two participants did not complete the study) [21]. Both studies were conducted at the Abbott Clinical Pharmacology Research Unit Waukegan, Illinois (single-site). No deaths or serious adverse event occurred during the study. Both studies confirmed the safety and bioequivalence of the low, high, and medium strengths. In addition to the bioavailability and bioequivalence studies recommended by the FDA, Abbott conducted five supplemental bioavailability and bioequivalence studies (only females participated in these supplemental studies): BP1 2020, BP1 2021, BP1 2022, BP1 2036, and FL1 2002 (Table 1) [21]. The reason for these supplemental studies was not clearly addressed in any of the documents submitted to the FDA. Nevertheless, the results all corroborated the safety of Synthroid.

Table 1: Completed bioavailability and bioequivalence studies for Synthroid

Drug (Manufacturer)	Identifier Code	Trial Phase (endpoint)	Study Design	Participants
Synthroid (Abbott Laboratories)	M01-323	Phase 1 (Bioequivalence and safety)	open-label, single-dose, randomized, three-period, six- sequence, cross-over (50 µg vs 100 µg vs 200 µg, each administered as 600 µg dose)	34
	BP1 2020	Phase 1 (Bioavailability and Safety)	2-way crossover, fasting, Synthroid vs. Levothyroxine (dose: 2x300µg)	29
	BP1 2021	Phase 1 (Bioavailability and Safety)	2-way crossover, fasting, Synthroid vs. Levothyroxine (dose: 2x300µg)	27
	BP1 2022	Phase 1 (Bioavailability and Safety)	2-way crossover, fasting, Synthroid vs. Levothyroxine (dose: 4x150µg)	28
	BP1 2036	Phase 1 (Bioavailability and Safety)	2-way crossover, fasting, Synthroid slow release vs. fast release tablets (dose: 4x150µg)	30
	FL1 2002	Phase 1 (Bioavailability and Safety)	2-way crossover, fasting, Synthroid vs. Levoxine (dose: 24x300µg)	30

Considerations to the US Food and Drug Administration Policy

Many considerations of changes have been made to the US' FDA's policy. The FDA has widened their mandate to survey the manufacturing and quality of drug products such as levothyroxine in manufacturing facilities domestically and overseas. Consequently, pharmacovigilance would increase in its frequency to ensure such quality control is followed. Another consideration is to remove the ambiguity regarding drug bioequivalence data and to make it more transparent for physicians and patients. This would help inform and make physicians more aware of prescribing a bioequivalent and interchangeable drug to a patient. This would also ensure the drug's safety in order to be administered as the reference-listed drug that would be compared against the reference drug. Concerns over bioequivalence and interchangeability of levothyroxine has bothered Amy Paulin, who is a State Congresswoman for the 88th New York State Assembly District, to the point of wanting companies to show bioequivalence data, even if the FDA does not require it, before selling in the New York market[22]. Providing bioequivalence studies to the public is currently not a practice when selling a drug. This allows companies to change their suppliers free-willingly in search of their active APIs and excipients, as long as they purchase their supplies from suppliers they listed in their Abbreviated New Drug Application. Lack of data transparency to the public has given drug manufacturers no incentive to ensure quality of their manufactured products. Inadequate Good Manufacturing Practices puts patients' health at risk of potentially being prescribed and administered a defective 'bioequivalent' medication.

Recommendations Concerning the Administration of Levothyroxine Preparations

As the administration of levothyroxine preparations has been a pressing issue, recommendations have been made to handle the issue. One of the recommendations that have been made is for patients to be maintained on the same formulation of levothyroxine. If a switch occurs among levothyroxine formulations, a blood test after 6 weeks is recommended to determine if any dosage adjustment is required[23]. Another recommendation suggested is to re-evaluate the determination of bio-equivalency between levothyroxine preparations. A re-evaluation would create a more accurate and reliable method of determining bio-equivalency between levothyroxine preparations to ensure drug safety and that the formulation is safe to use when administered to patients. Another recommendation suggested is to welcome more collaboration between professionals when introducing a new levothyroxine formulation to the market. Such collaboration would help circumvent insufficient communication and coordination of introducing a new formulation to the market. This would help ensure patients are receiving medication that has been carefully reviewed and tested for drug efficacy.

CONCLUSION

In conclusion, it is clear that the FDA used the 1997 FRN to expose unreliable manufacturers such as Forest Pharmaceuticals. By reclassifying levothyroxine products as new drugs, the FDA was able to regulate a market that seemed to operate beyond the purview of the law. The interchangeability of levothyroxine continues to be an ongoing issue. From issues concerning the physicochemical properties of levothyroxine to time affecting the potency of a levothyroxine batch, it is evident that bioequivalence between levothyroxine preparations is more difficult to establish in actuality. These issues, however, have created an open dialogue between healthcare professionals, stakeholders, patients, and regulatory agencies. Such dialogue is a sign that the priority remains the safety of patients and improvement of health outcomes.

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