Chapter 1

Designing a New Levothyroxine with Tightened Specification for the Modern Era of Management of Hypothyroidism

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The mainstay of the pharmacologic management of hypothyroidism is thyroid hormone replacement with levothyroxine (LT4), usually for life. Feedback systems within the hypothalamic-pituitary-thyroid axis are organised in such a way that even minor alterations in the administered dosage of LT4 can cause significant changes in the rate of secretion of thyrotropin, the main hormone which regulates the activity of the thyroid gland. LT4 has, therefore, been described as a "narrow therapeutic index drug". A new formulation (NF) with tightened specification has been engineered in collaboration with regulatory authorities to provide a more accurate and reproducible dose of LT4 throughout the patient's treatment, compared with earlier formulations of LT4. Switching to NF from an older formulation of LT4, therefore, helps to maintain strict control of the level of exposure of the patient

to administered LT4 during long-term treatment, which is crucial for maintaining a stable euthyroid state.

Introduction

Hypothyroidism arises when the secretion of thyroid hormones from the thyroid gland (thyroxine [T4] and triiodothyronine) is insufficient to meet the body's needs. The severity of hypothyroidism is defined according to thyroid hormone status, as described later in this chapter. Briefly, current guidelines for the management of hypothyroidism recommend that all patients with overt hypothyroidism and a proportion of patients with subclinical hypothyroidism require thyroid hormone replacement with levothyroxine (LT4), a pharmacological formulation of T4.[1–3] Treatment is usually for life, particularly concerning a patient with overt hypothyroidism, with periodic dosage adjustment to retain thyroid hormone levels within range.[4]

LT4 is described as a "narrow therapeutic index" drug in that even small variations in the administered dose of LT4 can induce clinically significant disturbances of systemic thyroid function.[5] The need for long-term accuracy, reproducibility and stability of the LT4 dosage during long-term treatment has led regulatory authorities and pharmaceutical companies to refine existing formulations of LT4.[6,7] This chapter describes the therapeutic rationale for the development of a new formulation (NF), which has been designed to meet these needs.

Why do we need an updated formulation of LT4 to manage hypothyroidism?

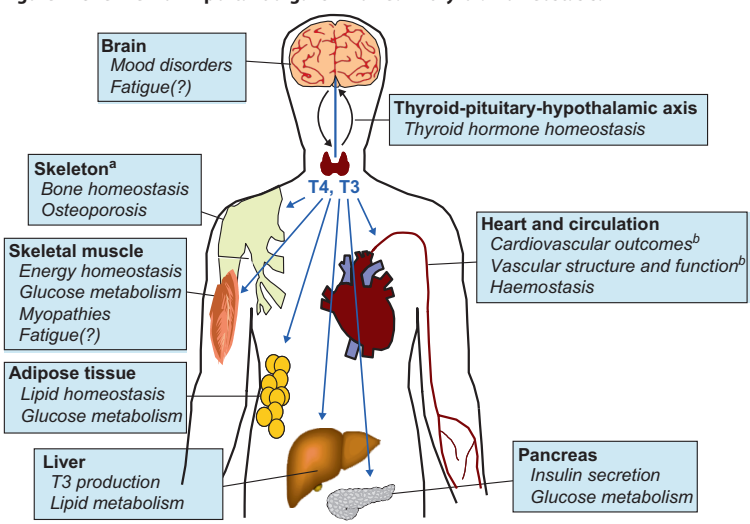
Overview of the regulation of thyroid homeostasis

Multiple feedback loops regulate the activity of the thyroid gland.[8] Briefly, thyrotropin-releasing hormone is released from the hypothalamus to act on the pituitary gland to increase the secretion of thyrotropin

(thyroid-stimulating hormone [TSH]). An increased circulating level of TSH then acts on the thyroid gland to increase the secretion of thyroid hormones (about 80% of which is T4, with the remainder being triiodothyronine [T3]). The resulting change in the level of thyroid hormones in the peripheral tissues impacts the function of every system in the body (Figure 1).[9] Specific deiodinases within these tissues deactivate thyroid hormones.

An increase in the thyroid hormone level also feeds back to the pituitary to reduce the secretion of TSH (and vice versa, with a lower thyroid hormone level increasing the secretion of TSH). In this way, a balance is achieved between the demand for and the secretion of thyroid hormones. Notably, the relationship between thyroid hormone secretion and TSH secretion is not linear: a given change in the level of thyroid hormones causes an increase in TSH secretion that is up to about 100-fold larger.[10] This has significant consequences for the management of hypothyroidism. Firstly, this is why TSH is used as the main clinical biomarker for assessing thyroid function, as it is more practical to measure relatively large changes in the TSH level, compared with much smaller changes in

Figure 1 Overview of important organs involved in thyroid homeostasis.



T3: triiodothyronine. T4: thyroxine. Adapted from reference 9 according to the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

the levels of thyroid hormones themselves, in the routine clinical practice setting (see also Chapters 3 and 4 of this book for information on the clinical management of hypothyroidism). Second, the nature of this feedback mechanism underpins the status of LT4 as a narrow therapeutic index drug. The large level of amplification involved in this circuit means that large and potentially clinically significant changes in the TSH level may arise following even tiny adjustments in the dosage of LT4. For a patient with hypothyroidism, such a scenario would tend to mitigate against the achievement of stable thyroid function during long-term treatment.[11]

LT4 as the mainstay of thyroid hormone replacement

T3 is the active form of thyroid hormone; T4 is converted to T3 in peripheral tissues by deiodinases.[12] The T3 then activates intracellular thyroid hormone receptors, which translocate to the nucleus to influence the transcription of multiple genes, especially those involved in metabolism and energy homeostasis. LT4 is preferred to preparations of T3 for therapeutic use mainly due to their respective pharmacokinetics. The plasma half-life of T4 is measured in days, compared with hours for T3; accordingly, LT4 is suitable for convenient, once-daily oral dosing with little change in circulating T4 levels during the dosing interval.[13] Chapter 8 of this book summarises the latest prospects for the therapeutic combination of T3 with NF for patients with hypothyroidism.

An increasingly challenging regulatory environment

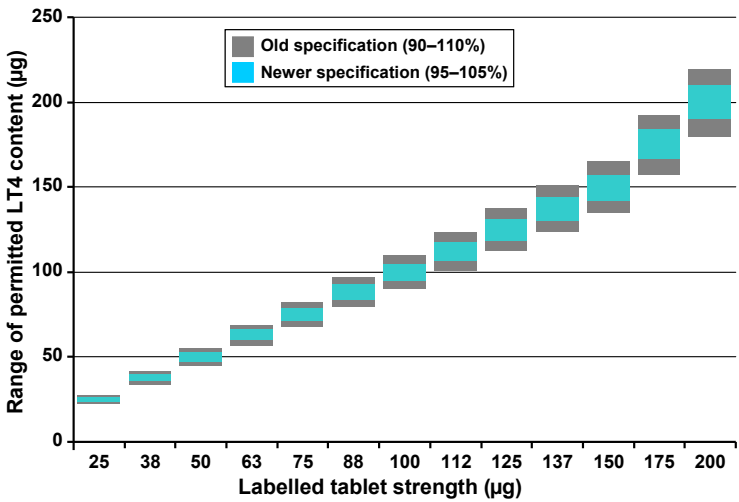
Regulatory authorities began to revise their guidance for the pharmaceutical industry on the pharmaceutical properties required for LT4 tablets from about the beginning of the second decade of this century.[6] These changes related to the accuracy of dosing and also to stricter standards for bioequivalence with a reference LT4 product to ensure more consistent absorption of T4 following ingestion of an LT4 tablet:

Accuracy and stability: The United States Pharmacopeia and National Formulary changed their guidance from "*Levothyroxine sodium tablets contain not less than 90.0 percent and not more than 110.0 percent*

of the labeled amount of levothyroxine sodium" to "*Levothyroxine sodium tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of levothyroxine sodium*".[14] An expert in the field noted at this time that the previous criteria of 90–110% potentially "*could result in differences in levothyroxine content approaching 20% from refill to refill*".[15] Other countries followed suit in subsequent years with requirements for actual vs. stated dosages tightened to 90–105% in the UK[16] and 95–105% in France, for example,[17] among others. Importantly, these criteria apply to the entire lifetime of a given batch of LT4; the French guidance, for example, states explicitly that the shelf life must be reduced if necessary to meet the standard.

Figure 2 illustrates the practical consequences of these new specifications regarding the actual range of amounts of LT4 that can be delivered via the new and old formulations. Note that the old specifications allowed considerable overlap between the actual content of adjacent tablet strengths if these were relatively closely spaced. In practice, this limited the number of dosage strengths that could be offered. The overlap

Figure 2 Ranges of permitted tablet content of levothyroxine (LT4) under newer and older specifications for manufacture of levothyroxine tablets.



Boxes represent ranges of permitted tablet LT4 content as shown for each tablet strength. See the text for a description of the relevant specifications.

is effectively removed according to the new criteria. As a result, tablets of NF containing LT4 in 13 distinct strengths (25–200 μg) shown in Figure 2 have been developed, providing enhanced flexibility and precision during initial dose titration and periodic adjustments in countries where these are available.

Bioequivalence: Establishing formal bioequivalence between two preparations of the same drug should ensure a minimum change in biological effect when switching a patient from one formulation to the other. Bioequivalence is assessed by comparing standard pharmacokinetic parameters between the two preparations, especially the area under the drug concentration-time curve (AUC), which is the principal measure of overall exposure to the drug. For most drugs, the upper and lower 90% confidence intervals for the geometric mean ratio of the AUC values for the two formulations must lie between 0.8 and 1.25 (often cited as 80–125).[18] Once again, the European criteria for new LT4 preparations are stricter, with a permitted range of 90–111.11% for the geometric mean ratio, consistent with its status as a narrow therapeutic index drug.[19] In the United States of America (USA), a narrow therapeutic index drug such as LT4 must meet *both* the standard 80–125% criteria and additional criteria derived from a calculation based on the within-subject variability of absorption of the drug.[20]

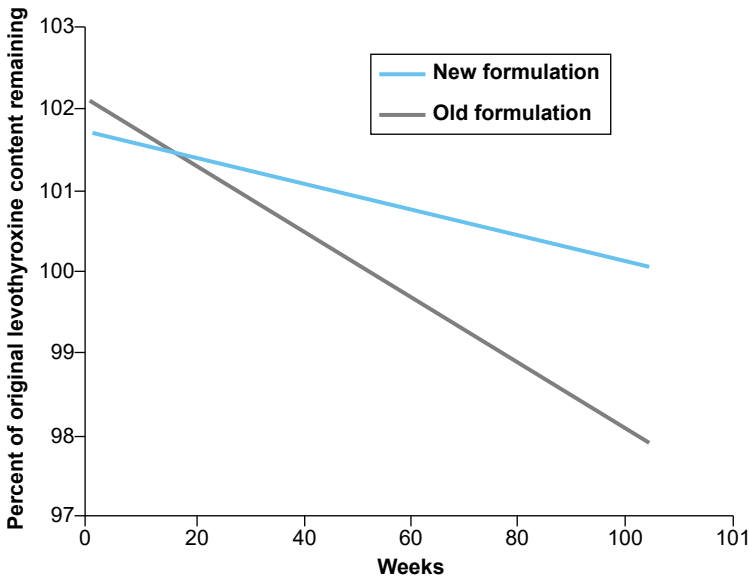
Development and properties of T4 new formulation

Historically, most pharmaceutical preparations have included a small amount of lactose as an excipient,[21] as the physical properties of lactose are well suited for constructing tablets containing low doses of an active ingredient.[21] The concentration of lactose used in medicinal formulations is normally too low to cause problems for the great majority of patients, even for people who are intolerant to lactose.[22,23] For example, a randomised trial in a population with confirmed lactose intolerance due to lactase deficiency showed that ingestion of a tablet containing 400 mg

lactose did not cause gastrointestinal side effects.[24] Nevertheless, case reports of gastrointestinal symptoms apparently associated with lactose-containing tablets have been published.[23] The NF tablet no longer contains lactose, as this has been replaced with mannitol and citric acid, which are other common and safe pharmaceutical excipients. Thus, NF is suitable for use for almost all patients with hypothyroidism, irrespective of their tolerance to lactose, and physicians can reassure their patients concerning this point.[6]

The inclusion of lactose also causes an additional problem associated with a spontaneous chemical reaction that occurrs slowly over time between lactose and LT4. In fact, the product of this reaction, levothyroxine-2-ketolactose, represents the main degradation product found, which emphasises the extent of the benefit of removing lactose in terms of the stability of the tablet. The shelf life of NF is 3 years in all climate zones, having been improved from 24 to 36 months in some hotter areas. All dosage strengths of the NF tablet meet the criteria for accurate dosing

Figure 3 Stability of the levothyroxine content of new formulation vs. old formulations.



Ten batches each were analysed.
Source: Merck healthcare KGaA, Darmstadt, Germany (data on file).

(described above) throughout this period. Figure 3 shows the improved stability of the active LT4 content of NF versus the older formulation.

Absorption of the NF

NF meets the strict bioequivalence criteria applicable to narrow therapeutic index drugs. Moreover, dose equivalence has been established between different tablet strengths so that different NF tablets can be combined to achieve a precise dosage, which can be useful when titrating the LT4 dose. Moreover, the specificity and quality of NF tablets renders the continuous use of these tablets imperative and makes even more strict the recommendation to avoid interchanging with generic or non-NF compounds. The studies underpinning these findings are described in detail in the following chapter.[25]

Summary and conclusions

The improvements made during the development of NF (summarised together in Table 1) have the potential to add precision and convenience during the initiation and maintenance of treatment for hypothyroidism

Table 1 Summary of improvements made during the development of a new formulation of T4 (NF) in comparison with the older formulation.

Attribute	Description
Lactose	No longer used in NF tablets
Dosage accuracy	Meets the specification of 95–105% of labelled tablet content at all dosage strengths
Stability	Shelf life of NF is 3 years in all climate zones (meets the above specification throughout this time)
Clinical	Meets enhanced European regulatory specifications relevant to narrow therapeutic index drugs for bioequivalence with the old formulation[a] Dose proportionality between tablet strengths facilitates combining different strengths to achieve precise dosing[a]
Tablets	Availability of up to 11 different tablet strengths from 25 µg to 200 g (as per the older formulation) facilitates switching and precise titration of the levothyroxine dose[b] Two additional strengths of NF are planned

Discussed in greater detail in Chapters [a]2 and [b]4.

for both the patient and their physician. Each can be confident that moving to the next tablet strength will indeed provide the promised incremental increase in the LT4 dose, and that prescribing the next treatment period will not incur significant variations between batches, irrespective of how long the tablets have resided on the pharmacy shelf. Finally, the availability of closely spaced dosage strengths and the ability to mix them to achieve a desired total dosage provide a new level of flexibility and precision for the prescribing physician.

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