A Review of the Pharmacokinetics of Levothyroxine for the Treatment of Hypothyroidism

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Abstract

Thyroxine hormone has been recognised since the early part of the nineteenth century and levothyroxine has been available since the mid-nineteenth century as a replacement for deficient thyroid hormones. While levothyroxine remains the staple treatment for hypothyroidism even to this day, its optimal use can be challenging. As is often the case with older drugs, the pharmacokinetics of levothyroxine is often under-appreciated or misunderstood and many factors influence the optimal dosing of levothyroxine. This article will review the pharmacokinetics of levothyroxine in the treatment of hypothyroidism and highlight major concepts that should aid both clinicians and researchers.

Keywords

Pharmacokinetics; drugs formulations; levothyroxine; intestinal absorption; interactions between drugs; hypothyroidism

Disclosure: Philippe Colucci, Corinne Seng Yue and Murray Ducharme are employees of Learn and Confirm Inc. and received funding from Institut Biochimique SA (IBSA). Salvatore Benvenga received from IBSA new L-thyroxine formulations for the conduct of clinical studies.

Received: 30 January 2013 **Accepted:** 17 February 2013 **Citation:** *European Endocrinology,* 2013;9(1):40–7 *DOI:10.17925/EE.2013.09.01.40*

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Role of the Thyroid Hormones

Thyroid hormones play a vital role in the human body and, as such, the absence of such hormones requires treatment. Generally, levothyroxine is used to treat thyroid hormone deficiency, and after a brief review of thyroid hormone physiology, this article will highlight what is known about the pharmacokinetics (PKs) of levothyroxine, as well as describe factors that can influence its PKs. The thyroid gland is responsible for the synthesis, storage and release of metabolic hormones including iodine-containing thyroxine (T_4) and triiodothyroxine (T_3). These hormones are crucial in the regulation of many metabolic processes and are vital for normal growth and development.[1] They are also involved in calorigenic, cardiovascular and metabolic effects. The hormones exert their effects presumably by activating gene transcription of messenger RNA and proteins. To do so, they enter the cell nucleus and bind to DNA-bound thyroid receptors, which regulate gene transcription.[1,2]

T_4 and T_3 Production and Feedback Loop Mechanism

Normally, the hormones secreted by the thyroid are regulated by the hypothalamic–pituitary–thyroid (HPT) axis through a negative feedback system. Low levels of circulating T_4 and T_3 initiate the release of thyrotropin-releasing hormone (TRH) from the hypothalamus and thyroid-stimulating hormones (TSH) from the pituitary. On interaction with its specific receptor, TSH stimulates the thyroid follicular cells to synthesise T_4 and T_3 and release them into the bloodstream. When circulating levels of T_4 and T_3 increase, they inhibit the release of TRH and TSH (i.e. negative feedback mechanism) thereby decreasing their own production.[1–4] The predominant hormone produced by the thyroid gland is T_4, with approximately 70–90 mcg of T_4 and 15–30 mcg of T_3 produced daily.[1,5] The production of the T_3 hormone by the thyroid gland is insufficient to meet the daily requirements of the organs in the body. Therefore, approximately 80 % of the body's required T_3 comes from peripheral conversion of T_4 to T_3.[4,6] Although both T_4 and T_3 are active, T_3 is more active as thyroid receptors within the cell nucleus have a 10-fold greater affinity for T_3.[2,4]

Indication and Dosage

Levothyroxine is a synthetic T_4 hormone that is biochemically and physiologically indistinguishable from the natural one, and it is administered when the body is deficient in the natural hormone.[7] Oral administration of levothyroxine is thus indicated for acquired primary (thyroidal), secondary (pituitary) and tertiary (hypothalamic) hypothyroidism.[8] It is also used to treat euthyroid goiters including thyroid nodules, subacute or chronic lymphocytic thyroiditis, multinodular goiter or for thyroid cancer patients who have undergone thyroidectomy, and as an adjunct to surgery and radioiodine therapy.[1]

For an average adult under the age of 50, the typical levothyroxine sodium dose is approximately 1.7 mcg/kg/day, which is equivalent to approximately 100–125 mcg/day. Older patients or patients with cardiac disease may require less levothyroxine and doses should be titrated at intervals of 4–6 weeks. Newborns, infants and adolescents require doses greater than 1.7 mcg/kg/day.The guidelines that were recently released by the American Association of Clinical Endocrinologists and American Thyroid Association task force on hypothyroidism in adults, in addition to diagnosis, include suggestions of therapy.[9]

Literature Search Method

A literature review was conducted in PubMed, Embase (1974 to week 47 of 2012) and Medline (1946 to third week of November 2012) using the terms 'levothyroxine' and 'pharmacokinetics'. The searches in Pubmed and Embase/Medline returned 1217 and 147 publications, respectively.

Pharmacokinetic Properties

Major characteristics of levothyroxine PKs are summarised in *Table 1* and are described in more detail below.

Absorption and Bioavailability

Levothyroxine is mainly absorbed in the small intestine, more specifically through the duodenum, jejunum and ileum.[10,11] Very little is absorbed in the stomach. Consequently, patients with shorter small intestines (bowel resection) have reduced absorption and require higher levothyroxine doses.[12] The time to maximum concentration (Tmax) occurs at approximately 2 hours in euthyroid volunteers while it is delayed to approximately 3 hours in hypothyroid patients.[13] Food also delays Tmax.[13,14]

The bioavailability of levothyroxine is approximately 60–80 % in euthyroid volunteers.[14–16] It may be slightly higher in hypothyroid and hyperthyroid patients,[15,16] and is decreased in the presence of food from 79 % under fasted conditions to 64 % under fed conditions for a 100 mcg dose.[14]

The absorption of levothyroxine appears to be influenced by gastric pH.[17,18] Centanni et al. demonstrated that in euthyroid patients suffering from nontoxic multinodular goiter, impaired gastric acid secretion or the use of omeprazole was associated with increased dosing requirements in order to adequately suppress TSH.[17] Similarly, Sachmechi and colleagues showed that chronic lansoprazole use in hypothyroid patients also resulted in increased levothyroxine dose requirements to maintain targeted TSH levels.[18]

Volume of Distribution

Levothyroxine has a limited volume of distribution, which has been reported to be 11.6 litres (L) in euthyroid volunteers and 14.7 L in primary hypothyroid subjects.[19] This is approximately equivalent to the extracellular fluid volume of the body.

Metabolism

Although T_4 is subject to multiple metabolic reactions,[20–22] the main metabolic route for T_4 involves deiodination reactions (removal of iodine) by deiodinase enzymes.[23–25] Removal of iodine from the carbon 5 of the outer ring transforms T_4 to T_3, thus T_4 can be regarded somewhat as a pro-hormone for T_3.Deiodination of the inner ring of T_4 can also occur, leading to the formation of inactive reverse T_3 (rT_3). Approximately half of deiodinised T_4 is metabolised to rT_3 and half to T_3.[25,26] Both T_3 and rT_3 are further metabolised to diiodothyronine (T_2), iodothyronamine (T_1) and reverse T_2 and T_1.[25,26]

Elimination

The daily turnover rate for T_4 is approximately 10 % while it is approximately 50–70 % for T_3, with a slightly faster turnover rate in normal volunteers compared with patients with primary hypothyroidism.[1,2] This equates to a half-life for T_4 of 7.5 days in hypothyroid patients and 6.2 days in euthyroid individuals, while the T_3 half-life is approximately 1.4 and 1.0 days for hypothyroid and euthyroid volunteers, respectively.[19] Clearance for T_4 was similar with 0.056 and 0.054 L/h in hypothyroid and euthyroid subjects, respectively.[19] These values are similar to other values reported in hypothyroid patients (0.0385 L/h/70 kg)[27] and in normal control subjects (0.053 to 0.064 L/h).[28,29]

Protein Binding

Both T_4 and T_3 are highly bound to plasma proteins at greater than 99.8 % (i.e. unbound T_4 = 0.02–0.03 %; unbound T_3 = 0.2 %) in both euthyroid and primary hypothyroid volunteers.[1,19,30,31] Both T_4 and T_3 bind predominantly (>80 %) to thyroxine-binding globulin (TBG), and to a lesser extent to thyroxine-binding prealbumin and albumin.[1,30] Benvenga and Robbins have also demonstrated binding to lipoproteins such as high-density lipoprotein.[32,33] The T_3 affinity for binding to these proteins is approximately one-thirtieth that of T_4,[34] which explains the higher turnover rate of T_3 compared with T_4.

Table 1: Summary of Levothyroxine PK

Pharmacokinetic Characteristic	Description
Main site of absorption	Small intestine (jejunum and ileum)
Bioavailability	70–80 % in euthyroid person; may be slightly higher in hyperthyroid patients
Tmax	2–3 hours
Vd	11–15 L
Protein binding	T_4 >99.9 % T_3 = 99.8 %
T1/2	T_4 = 6.2 and 7.5 days in euthyroid and hypothyroid patients, respectively T_3 = 1.0 and 1.4 days in euthyroid and hypothyroid patients, respectively
CL	T_4 = 0.055 and 0.038 L/h in euthyroid and hypothyroid patients, respectively

Vd = Volume of distribution; L = Litres; CL = Clearance

Transporters/Cytochrome Enzymes

Active transport of thyroxine into cells has been recognised for some time.[35,36] *In vitro* studies have shown that organic anion transporting polypeptides (OATP) (such as OATP1A2, OATP1B1, OATP1C1, etc.), monocarboxylate transporter and sodium-taurocholate cotransporting polypeptide are involved at different levels.[37–41]

However, few articles have been published on the *in vivo* significance of these transporters on the PK of levothyroxine. Lilja et al. demonstrated the effects of the influx intestinal OATP transporter inhibition by grapefruit juice consumption on levothyroxine absorption.[42] They concluded that grapefruit juice had only a minor effect if any on levothyroxine absorption (AUC0-6 dropped by 9 % and Tmax was slightly delayed).[42]

A transporter that may be induced by levothyroxine is PgP (*ABCB1* gene). Jin et al. published results that showed that cyclosporine A trough concentrations were lower in patients taking levothyroxine. In addition, the expression of this transporter was increased and oral cyclosporine A concentrations and bioavailability were lower in rats treated with levothyroxine.[43]

PK Properties in Special Populations

Table 2 summarises the effects of different conditions on the PK of levothyroxine and additional details are presented below.

Renally Impaired Patients

The kidney plays a significant role in the peripheral metabolism of T_4 to T_3.[1] Therefore, this metabolic route is significantly reduced in renally impaired patients, partially due to accumulated uremic toxins.[44,45] In patients with renal disease, there is a reduction in total and free T_3 while T_4 is less affected;[46,47] however, some patients with end-stage

Table 2: Pharmacokinetics of Levothyroxine in Special Populations

	Bioavail-ability	Metabolism (T_4 to T_3)	Protein Binding	Elimination	TT_4	TT_3	fT_4	fT_3
Renal impairment		↓	↓			↓		↓
Hepatic impairment (cirrhosis)		↓	↓		↑	↓	↑	↑↓
Elderly	↓	↓		↓		↓		↓
Children				↑	↓			
Obesity					↑↓	↑↓		
Pregnancy				↓			↓	
Gastrointestinal disorders	↓							
Food	↓							

↑ = increase; ↓ = decrease; ↑ ↓ = contradiction in literature about impact. TT4 and TT3= total T4 and total T3; fT4 and fT3= free T4 and free T3.

renal disease are also diagnosed with hypothyroidism.[48] It has also been reported that other metabolic routes may be enhanced, resulting in higher T_3 sulphate concentrations.[49] The proteinuria associated with the nephrotic syndrome may cause urinary loss of the thyroid hormones bound to the thyroid hormone transport proteins.[50,51]

The volume of distribution of thyroxine is also increased in patients with renal failure, which is probably due to the decreased protein binding of thyroxine.[52] Haemodialysis does not have an impact on levothyroxine requirements in this patient population.[47,48] However, kidney transplantation has been shown to affect the levels of thyroid hormones.[47] Some authors report that levels of T_3 increase with time after transplantation and doses of levothyroxine can consequently be reduced,[45,47] while others report the contrary.[53] The increased levothyroxine dose could also be due to drug–drug interactions with the medications patients are required to take after kidney transplantation.[47]

Hepatically Impaired Patients

The liver is a major site for T_4 deiodination to T_3.[1,2] In addition, T_3 and T_4 are conjugated with glucuronic and sulphuric acids and then excreted in the bile.[6] Approximately 20 % of T_4 is eliminated in faeces.[1] Therefore, it is expected that patients with hepatic impairment would have different levels of circulating T_4 and T_3 compared with patients with normal hepatic activity. Indeed, several studies have reported similar or higher levels of total and free T_4,[54,55] decreased levels of total and free T_3 and elevated concentrations of rT_3[56–59] in patients with severe cirrhosis compared with normal patients. Other authors have not shown significant reduction in T_3 concentrations in patients with different degrees of liver impairment except when patients had severe cirrhosis.[60]

The clinical impact of severe cirrhosis on thyroid hormone levels is also influenced by other factors, such as lower levels of thyroxine binding proteins such as albumin. Overall, this possibly leads to an increase in free T_4 concentrations or the ratio of free T_3 to bound T_3, meaning that despite overall lower levels of T_3, more free T_4 and T_3 is available. Thus, because levothyroxine is a low-extraction drug, changes in protein binding will affect total levels but not free levels of hormone. Furthermore, increasing the dose of levothyroxine may not compensate for the lack of liver metabolism of T_4 to T_3.

Obesity

TSH values are increased in obese patients, which could be attributed to leptin, a hormone produced by adipose tissue that may increase TSH secretion.[61,62] Therefore, in such patients, increased levels of TSH do not necessarily indicate hypothyroidism, and TSH should not be the only criteria used to adjust doses.

Some authors have reported higher circulating concentrations of T_4 and T_3 in obese patients while others have reported lower levels.[63,64] Santini et al. reported the lack of a correlation between serum leptin concentrations and the total dose of levothyroxine administered and that adipose tissue had a minor impact on levothyroxine requirements.[65] The authors also indicated that lean body mass was superior to actual weight as a predictor of dosage, which is in line with levothyroxine's small volume of distribution. Greater dose requirements in obese patients are probably attributed to a slightly higher volume of distribution (i.e. higher lean body mass and peripheral mass) compared to non-obese patients rather than to a greater overall weight (fat weight). If weight is used to determine a starting dose in obese patients, total weight may lead to supra-therapeutic doses, therefore using lean body mass might be a better alternative.[65]

Pregnancy

Following conception in euthyroid women, TBG increases quickly with a rise in total T_4 concentrations, and decreases in free T4 and TSH in the first trimester.[66] T_4 production increases 20–40 % in the early part of the first trimester and this continues throughout the pregnancy.[67] In hypothyroid women who become pregnant, T_4 requirements are also similarly increased, often necessitating an increase in levothyroxine dosage.[68] It should be noted that as TSH values are normally lower in the first trimester, increased T_4 requirements may not be recognised if TSH is the only marker used to adjust levothyroxine administration doses. Soldin et al. reported that levothyroxine clearance was faster in non-pregnant women at 7.0 L/h versus 4.5 L/h in pregnant women, despite similarities in Tmax and Cmax.[67] In addition, PK parameters in pregnant women appeared to be more variable.[67]

Children

Heskel et al. reported a shorter half-life for T_4 in euthyroid children compared with adults (4.95 days for children and almost 7 days in adults).[69] They concluded that when considering weight, there was a decreased pool of T_4 and an increased elimination rate of thyroxine. Furthermore, Mainwaring et al. reported a shorter half-life for T_3 in children undergoing cardiopulmonary bypass compared with adults having the same procedure (seven hours versus close to one day).[70] According to the American Thyroid Association[71] and the levothyroxine product monograph,[72] infants and children require higher doses per

Table 3: Drugs Interfering with Thyroid Function or with Levothyroxine Pharmacokinetics

Drug or Drug Class	Relative Bioavailability	Synthesis	Metabolism	Protein Binding	Thyroid-stimulating Hormone	Overall Effect on Thyroid Hormones		Clinical Recommendation
						Total T_4	Free T_4	
Aluminium hydroxide	↓					↓		Avoid concomitant use (separate intake by 4 to 6 hours)
Amiodarone	↑↓	↑↓	↓			↔↑↓		Monitor thyroid function
Anabolic steroids				↓		↓	↔	Lower dose may be necessary
Androgens				↓		↔	↔	Lower dose may be necessary
Beta blockers	↓[a]	↓[a]	↓[a]	↓[b]		↓ (transient[b])		Monitor thyroid function
Calcium carbonate/citrate/acetate	↓					↓		Avoid concomitant use (separate intake by 4 to 6 hours)
Carbamazepine			↑	↓		↓	↓↔	Monitor thyroid function
Cholestyramine	↓					↓		Avoid concomitant use (separate intake by 4 to 6 hours)
Cimetidine	↓					↓		Increase levothyroxine dosage
Colsevelam	↓					↓		Avoid concomitant use (separate intake by 4 to 6 hours)
Dopamine (≥0.4 mcg/kg/min)					↓	↓ (transient)		Dose modification unnecessary
Ethinyl oestradiol				↑		↑		Higher dose may be necessary
Ferrous sulphate	↓					↓		Avoid concomitant use (separate intake by 4 to 6 hours)
Fluorouracil				↑		↑	↔	Dose modification unnecessary
Furosemide (high dose)				↓		↓ (transient)	↑ (transient)	Dose modification unnecessary
Glucocorticoids (dexamethasone ≥0.5 mg/day or hydrocortisone ≥100 mg/day)			↓ (initial)	↓	↓ (transient)	↓ (transient)		Lower dose may be necessary
Heparin				↓		↓ (transient)		Dose modification unnecessary
Heroin				↑		↑	↔	Monitor thyroid function
Iodide		↑↓				↓		Monitor thyroid function
Lithium		↓				↓		Monitor thyroid function
Methadone				↑		↑	↔	Dose modification unnecessary
Mitotane				↑		↑	↔	Dose modification unnecessary
Nicotinic acid				↓		↓		Dose modification unnecessary
Octreotide (≥ 100 mcg/day)								No dose modification necessary

Table 3: (Continued)

Drug or Drug Class	Relative Bioavailability	Synthesis	Metabolism	Protein Binding	Thyroid-stimulating Hormone	Overall Effect on Thyroid Hormones		Clinical Recommendation
						Total T_4	Free T_4	
Orlistat	↓					↓		Monitor thyroid function
Phenobarbital			↑			↓		Increase levothyroxine dosage
Phenytoin			↑	↓		↓	↔↓	Monitor thyroid function
Phosphate binders	↓					↓	↓	Separate intake by four or more hours
Proton pump inhibitors (omeprazole, lansoprazole)	↓					↓		Increase levothyroxine dosage
Rifampin			↑			↓		Increase levothyroxine dosage
Salicylates (>2 g/day)				↓		↓ (transient)	↓ (long-term use)	Dose modification unnecessary
Sucralphate	↓					↓		Separate intake by four or more hours
Sulphonamides		↓				↓		Monitor thyroid function
Tamoxifen				↑		↑	↔	Higher dose may be necessary
Tolbutamide		↓				↓		Monitor thyroid function

↔ = unchanged, ↑ = increase, ↓ = decrease, ↑↓ = either increase or decrease; a = propranolol; b = acebutolol, oxprenolol, timolol.

weight or per body surface area compared with adults.[73] The typical dose can be as high as 10–15 mcg/kg/day for infants from 0–3 months old and it decreases towards adulthood where the typical dose is 1.7 mcg/kg/day.

Elderly

In healthy elderly individuals, secretion of T_4 and T_3 and metabolism of T_4 to T_3 are reduced while rT_3 levels appear to increase.[74,75] Accordingly, the elimination half-life for T_4 is longer and reported to be 9.3 days in patients older than 80 years old.[76] Absorption of T_4 is also slightly lower for patients above 70.[77] Although T_4 concentrations do not appear to be decreased in older euthyroid patients, total and free T_3 concentrations are reportedly lower in individuals 61–90 years old compared with younger individuals[74], which is expected due to their decreased metabolism. Therefore, measurements of only T_4 may be insufficient to explain changes in elderly patients' thyroid function.

Gastrointestinal Disorders

Certain gastrointestinal disorders, including celiac disease[78] and *Helicobacter pylori* infection[17], can impede the absorption of levothyroxine. As levothyroxine is mainly absorbed through the small intestine, its absorption is compromised in patients with coeliac disease.[78] Higher levothyroxine doses were reportedly required in patients with coeliac disease and when patients followed a gluten-free diet, levothyroxine dose requirement was reduced.[78,79] *H. pylori* infection causes chronic gastritis and affects gastric acid secretion in the stomach.[17] Levothyroxine doses have been reported to be higher in hypothyroid patients with this disease.[17,80] However, following resolution of the infection, Bugdaci et al. recommend that doses be lowered.[80] Other gastrointestinal disorders such as inflammatory bowel disease, lactose intolerance and atrophic gastritis have also been demonstrated to affect levothyroxine absorption.

Drug and Food Interactions

Many substances are known to influence T_4 or T_3 levels and the impact appears to be more significant in hypothyroid patients being treated with exogenous supplementation compared with patients without thyroid pathology, probably due to their intact feedback mechanisms. In addition, interactions with levothyroxine can also occur indirectly via modulation of the HPT axis. All these will be described below and are summarised in *Table 3*.

Food

The oral absorption of levothyroxine can be impaired by various substances, such as food[13,81–83], soy bean,[84–91] papaya[92] and grapefruit.[42] Benvenga and colleagues have demonstrated that coffee can also impair the absorption of certain levothyroxine formulations.[93,94]

Drugs

Drugs can alter the PKs of thyroid hormones in various ways.[95] Drugs that decrease TSH secretion (dopamine,[96–100] glucocorticoids,[101,102] octreotide[103,104] and rexinoids[105,106]) lead to decreased thyroid hormone concentrations, while thyroid hormone synthesis is interfered with by other drugs,[107] such as lithium, iodine[108], tolbutamide, sulphonamides and amiodarone.[109,110]

Proton-pump inhibitors, such as omeprazole[17] and lansoprazole,[18] have also been shown to influence the absorption of levothyroxine, as

assessed by TSH levels in patients, since normal gastric acid secretion plays a major role in the absorption of thyroxine. Interestingly, others found that in healthy volunteers, famotidine and esomeprazole had no such effect.[111] Aluminium hydroxide[112–114], dietary fibre[115], calcium carbonate,[116–119] calcium citrate,[120] calcium acetate, ferrous sulphate,[121–123] cholestyramine[124] and colsevelam[125,126] decrease levothyroxine absorption by binding to it and forming complexes that are not absorbed. Sucralphate[127] may decrease levothyroxine absorption by interfering with its intra-luminal transport or by binding to it.[82].Other products such as phosphate binders,[126,128,129] orlistat[130] and cimetidine[131] also appear to decrease the absorption of levothyroxine, although the interaction mechanism/s is/are not as clearly defined.

Drug interactions can also influence other PK processes. For instance, the administration of beta blockers such as acebutolol, oxprenolol and timolol appear to modify the extracellular distribution of T_3, thereby decreasing T_3 levels.[132] Changes in protein binding can also influence the PK of levothyroxine, as decreased protein binding is associated with greater levels of free levothyroxine, which is then more readily eliminated from the systemic circulation. Drugs that decrease levothyroxine protein binding include carbamazepine,[133] androgens, anabolic steroids,[134,135] and nicotinic acid.[136,137] Certain drugs are associated with transient increases in free T_4 levels due to inhibition of protein binding,[107] including high-dose furosemide,[138] salicylates[139–141] and heparin.[140,142] Conversely, drugs that increase protein binding are associated with a reduced clearance of levothyroxine. Such drugs include ethinyl oestradiol,[143–145] tamoxifen,[146] heroin, methadone,[147–150] mitotane and fluorouracil.[151,152]

Finally, some drug interactions with levothyroxine can be explained by an effect on its metabolism, such as the extrathyroidal conversion rate of T_4 to T_3. Certain drugs, such as propranolol[28,29,153,154] and amiodarone,[107] reduce this metabolism. Conversely, carbamazepine,[133,155–158] phenobarbital,[159,160] rifampin[107] and phenytoin[155,161] induce liver microsomal enzymes and increase this peripheral metabolism.

Available Formulations

Commercial levothyroxine oral formulations available in North America and Europe include powders for intravenous solutions, tablets (e.g. Synthroid®, Levo-T™, Levothroid®, Levoxyl®, Unithroid®, Eltroxin®, Elthyrone®, Euthyrox®, Eferox®, Berlthyrox®, Letrox®, Tirosint®), soft gel capsules (Tirosint®) and oral solutions (Eltroxin®, Tirosint® oral drops and Tirosint® oral solution in unit-dose ampules).

There are advantages and disadvantages that are unique to the formulation type and not to levothyroxine per se. For instance, while tablets and capsules offer the advantage of precise dosing, solutions and liquids can be easier to swallow for children or the elderly. Formulation differences that are specific to levothyroxine also exist. The influence of pH on dissolution profiles of tablets and soft gel capsules is dissimilar,[162] as well as the negative impact of coffee intake on levothyroxine absorption.[93,94]

Bioequivalence

The existence of multiple levothyroxine formulations is also the result of the availability of many generic versions of these compounds. Many studies have been published describing comparisons of the PK properties of various levothyroxine formulations[163–181] and various approaches have been employed since bioequivalence assessments of levothyroxine are complicated by baseline levels, feedback mechanisms and by the fact that levothyroxine is considered by some to be a 'narrow therapeutic index' (NTI) drug, which some believe merit more stringent criteria (confidence intervals of 90–111 % rather than the standard 80–125 %, or stability throughout the shelf-life of +/-5 % instead of +/-10 %). For this reason, specific guidelines pertaining to assessing the bioequivalence of levothyroxine formulations have been published, in particular by the US Food and Drug Administration (FDA).

Current regulatory guidelines published by the FDA recommend that bioequivalence of levothyroxine formulations be assessed by comparing PK measures of T_4.[182] The underlying assumption regarding the use of T_4 rather than TSH or T_3 is that systemic T_4 levels reflect the levels at the site of action, and that a relationship exists between the efficacy and safety of the product and its systemic levels. Despite TSH sensitivity to changes in thyroid hormone level, TSH is not used to assess bioequivalence of thyroid formulations because it is a secondary response to levothyroxine and there is a significant time delay between the administration of exogenous levothyroxine and the changes noted in TSH levels. In addition, it is simply not a direct measure of levothyroxine-administered product, as are baseline-adjusted T_4 concentrations.

Because levothyroxine is an endogenous compound, it is important to take baseline levels into consideration when performing bioequivalence assessments to avoid biasing comparisons which can lead to failure in distinguishing true differences between formulations.[183] Current FDA bioequivalence guidelines require that supra-therapeutic doses of levothyroxine (600 mcg) be administered and that levothyroxine PK parameters be corrected for individual baseline values. This minimises the effect of endogenous concentrations on bioequivalence assessments[182,184] by ensuring a high signal (concentrations related to exogenous levothyroxine) to noise (endogenous levels) ratio.

In addition to some of the recommendations described above, the FDA also stipulates that a levothyroxine product must have a 95–105 % potency specification over its entire shelf-life instead of previously accepted potency limits of 90–110 %.[185] This was established to ensure greater consistency in levothyroxine administered to patients and to reduce possibly large fluctuations in drug concentrations.

Thus, recommendations from current regulatory guidelines regarding study design and baseline adjustment of PK parameters ensure that a conservative approach to bioequivalence of levothyroxine formulations is adopted.

Summary

Although levothyroxine has long been a mainstay in the treatment of hypothyroidism, its optimal use often remains elusive. Not only are thyroid hormones levels governed by sensitive and complicated feedback mechanisms, but they are also subject to the influence of disease, the intake of food and the use of concomitant medication. While these competing factors can pose a challenge for clinicians, a thorough comprehension of these elements as well as other PK considerations will ultimately be beneficial for the patient. ■

For details about the basic and clinical thyroid effects of tyrosine kinase inhibitors, including enhanced dose of levothyroxine, the reader is referred to a review just released by Makita and Iiri.
(Ref: Makita N, Iiri T, Tyrosine kinase inhibitor-induced thyroid disorders: a review and hypothesis, *Thyroid*, 2013 Feb;23(2):151–9.)

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