Two Non-Tablet Oral Formulations of L-Thyroxine

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Increased knowledge of the pharmacokinetic characteristics of orally administered levothyroxine (L-T_4) has improved individualization of dosing regimens. However, up to 40–45% of patients, depending on the leading cause of hypothyroidism, are still over- or, more often, undertreated. Unintentional non-adherence to L-T_4 replacement therapy includes all situations of unintended drug–drug and drug–food interactions as well as fasting conditions that are not necessarily respected by patients. The non-tablet L-T_4 soft-gel capsules and solution have proven bioequivalence with the usual L-T_4 tablet Princeps and generic formulations. Clinical studies have suggested higher performance of non-tablet formulations than tablet in those patients with suboptimal adherence.

levothyroxine hypothyroidism soft-gel capsule oral solution pharmacokinetics drug–food interactions gastrointestinal conditions switch

1. Introduction

Thyroid hormones play a critical role in the human body and, as such, if such hormones are absent, they must be replaced. Levothyroxine (L-T_4) is the recommended replacement thyroid hormone for both primary and central hypothyroidism. Since the 1970s, most hypothyroid subjects worldwide have been treated with the usual oral tablet L-T_4; thus, it is in the first decile of most prescribed medications in Western countries [1][2]. Levothyroxine is a critical-dose drug since even slight variations in blood concentration may determine treatment failure (i.e., incomplete replacement or iatrogenic thyrotoxicosis). Then, individualized L-T_4 treatment is required and a close clinical follow-up to avoid under- and overtreatment of patients.

The daily dose of L-T_4 depends on the leading cause of hypothyroidism (mostly primary hypothyroidism) as well as on several potential determinants, mainly patients' lean body mass, which is not routinely measured in clinical practice, and the therapeutic goal (i.e., replacement or Thyreo-Stimulating Hormone (TSH)-suppressive therapy in thyroid cancer patients, when needed). Recent improvement in knowledge concerning the pharmacokinetic characteristics of orally administered L-T_4 has improved individualization of dosing regimens. However, up to 40–45% of patients, depending on the leading cause of hypothyroidism, are still over- or, more often, undertreated [3], and nonadherence only accounts for less than 17% of the cause of poorly targeted dosing regimens [1][2]. Unintentional non-adherence to L-T_4 replacement therapy includes all situations of unintended drug–drug and drug–food interactions, as well as fasting conditions that are not necessarily respected by patients despite it being well known that undergoing L-T_4 replacement therapy in fasting conditions improves intestinal absorption of the

active ingredient [4]. Besides these causes of increased doses of L-T_4, some conditions and disorders may enhance daily L-T_4 requirement by affecting its intestinal absorption, including celiac disease, lactose intolerance and infections, especially *Giardia intestinalis* infection [2][4]. In this specific context, it has to be remarked that the overall information concerning those factors with the potential to affect L-T_4 absorption refers only to tablet formulation. Indeed, this is the reason why new non-tablet formulations of L-T_4 were introduced some years ago. Furthermore, numerous studies have been published during the last decade in this field and reported that hypothyroid patients with not-on-target TSH for tablet L-T_4 can experience optimal (or at least improved) thyroid hormonal balance after switching to liquid or soft-gel L-T_4 formulation despite an unchanged dose. In contrast, to the best of researchers' knowledge, no papers have recorded an improvement of control of hypothyroidism when a patient switches from soft gel or liquid to tablet L-T_4.

Alongside this increasing information, whether such improvement in dosing regimens and pharmacokinetic stability is or is not associated with substantial improvement in clinical symptoms and number and frequency of both over- and undertreated patients remains debated. In this regard, the current entry was designed to summarize pharmacokinetics, drug and food interactions and clinical data focusing on two new L-T_4 preparations, i.e., liquid and soft-gel capsule, in healthy volunteers and patients with primary hypothyroidism.

2. Bioequivalence Studies with Soft-Gel Capsule and Oral Liquid Formulation

Because levothyroxine pharmacokinetics is highly variable due to the influence of several physiological (e.g., old age, pregnancy) and pathological (liver or kidney impairment, morbid obesity, gastrointestinal disorders) conditions, as well as numerous drug–drug and drug–food interactions, reaching bioequivalence between Princeps and the numerous formulations currently marketed may appear as a challenge. Indeed, results of the pharmacokinetic studies involving L-T_4 need to be carefully interpreted, considering baseline hormone concentration and central nervous system feedback mechanisms. In this regard, pharmacokinetic studies have focused on L-T_4 serum concentrations rather than TSH, the target biomarker in clinical practice.

Numerous studies, most of them conducted in healthy euthyroid subjects, have confirmed bioequivalence between, separately, the classical sodium levothyroxine formulation and L-T_4 soft-gel capsule or the latter and the solution. Overall rate and extent of exposure, as well as elimination half-life (ranging from 6 and up to 9 days) were not statistically different among the preparations but faster (approximately 30 min earlier) onset of absorption was noted with the new oral liquid L-T_4 versus gel caps and the Princeps tablet formulation in a few studies [5]. Low- (50 µg), medium- (100 µg) and high (200 µg)-strength soft-gel capsules of L-T_4 were bioequivalent to the European reference tablet, showing proportionality, at a dosage of 600 µg in healthy volunteers, the latter dosage being required by many agencies in order to achieve L-T_4 concentrations sufficiently above the endogenous base [6]. In the study, it was interesting to note that the 90% confidence interval (CI) to demonstrate bioequivalence was set at 80–125%, and that the authors observed as much as 15% intra-individual variability in their study enrolling only healthy subjects despite stable L-T_3 concentrations and similar tolerance between the respective formulations [6]. Two distinct soft-gel capsules (the “old” one and the “new” one manufactured using the new Food & Drug

Administration Potency guidelines) were shown to be bioequivalent with each other and with the American tablet formulation (Synthroid), using bioequivalence 90% with a confidence interval of 80–125% for mean ratio of the serum L-T_4 systemic exposure [7]. Finally, bioequivalence, as assessed by using the 90% CI for mean ratio of the systemic exposure (i.e., C_{max} and AUC_{0-48}) was also confirmed between the two new oral formulations, oral solution and soft-gel capsules, in a recent crossover study conducted in healthy subjects taking a single oral dose of 4 × 150 µg with or without water and using current European Medicine Agency (EMA) prespecified bounds of 90.00 to 111%, as recently required for bioequivalence studies [8].

3. The Oral Solution and Soft-Gel Capsule Formulations Display Better Pharmacokinetic Profiles than the Usual Tablets of Levothyroxine in the Case of Drug–Drug or Drug–Food Interactions

It is known that several factors can interfere with intestinal absorption of L-T_4, i.e., food ingestion, dietary fiber, coffee, breakfast beverages and drugs. Numerous drug–drug and drug–food interactions with L-T_4 tablets have been identified and reports on them have been published over the past 30 years, as summarized in **Table 1** [9][10]. Most of these drug–drug and drug–food interactions led to L-T_4 intestinal malabsorption and further increase in TSH level, consistent with under-substitution despite stable dosage of L-T_4. One of the most clinically relevant drug–drug interactions in this setting involves proton-pump inhibitors, which induce clinically significant L-T_4 malabsorption by modifying gastric pH [11][12]. In a retrospective real-world evidence study in primary care, drug–drug interactions involving proton-pump inhibitors accounted for 88% of all drug–drug interactions reported with levothyroxine tablets, oral solution or soft-gel capsules [13]. Such interactions with proton-pump inhibitors may be solved by switching from the Princeps levothyroxine tablet to the new soft-gel capsule, as observed in a recent case report of a woman in whom an absorption test displayed a 48% increase in systemic exposure of L-T_4 along with faster intestinal absorption [11]. In addition, despite that TSH variation in serum did not differ significantly between the tablet formulation and the, soft-gel capsule and oral solution, separately, the latter allowed more a stable dosing regimen and less dose adjustment, consistent with a more stable pharmacokinetic profile in the case of drug–drug interactions in the clinical setting [13]. In another study conducted in healthy volunteers, bioequivalence between L-T_4 tablets and soft-gel capsules was lost when taken with esomeprazole, with a 16% decrease in the peak serum concentration and systemic exposure of L-T_4 tablets as compared to the soft-gel capsules [12]. Calcium salt supplementation, especially in postmenopausal women, may increase the risk of L-T_4 malabsorption and suboptimal TSH balance in hypothyroid patients. Despite that this drug–drug interaction may prevent delayed calcium salt ingestion, it is not always satisfactory as compared to switching from the tablet to the new oral solution or L-T_4 soft-gel capsules, as recently observed in a clinical study involving 50 hypothyroid postmenopausal women taking L-T_4 tablet therapy [14].

Table 1. Impact of drug and food on levothyroxine absorption [9][10].

Interactions with Drugs	Interactions with Food
• Acid suppression therapies (proton-pump inhibitors, H2 receptor antagonists, sucralfate) • β-blockers • Bile acid sequestrants (cholestyramine, colestipol and colesevelam) • Calcium salts (carbonate, citrate, and acetate) • Cation exchange resins • Charcoal • Chromium • Ciprofloxacin • Ferrous sulfate • Lanthanum • Multivitamins (containing ferrous sulfate or calcium carbonate) • Oral bisphosphonates • Orlistat • Phosphate binders (sevelamer, aluminum hydroxide) • Polystyrene sulfonate • Rifampicin • Raloxifene • Simethicone • Tricyclic antidepressant	• Coffee • Fiber • Grapefruit • Ingestion with a meal • Papaya • Soybeans and soy

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uboptimal compliance with L-T_4 ingestion as they have to postpone breakfast by at least 30 min [15]. The TICO randomized, double-blind, placebo-controlled crossover trial suggested that liquid L-T_4 solution with ethanol should be ingested directly with or 30 min before breakfast with no statistical difference in TSH, free T_3 and free T_4 levels, thus potentially improving therapeutic compliance. The use of L-T_4 liquid formulation without ethanol concomitantly with

breakfast, however, remains off-label. This observation is of remarkable clinical relevance since suboptimal adherence to L-T_4 therapy is more likely to cause TSH variation over time [15][16]. Patients undergoing treatment with L-T_4 are usually asked to ingest the drug in the morning, at least 30 min before having breakfast, because a significantly decreased L-T_4 absorption was reported with food when patients are treated with the usual tablet [17][18]. However, oral solution without ethanol should still be preferred in patients in whom even small changes in the free fraction of T_3 or T_4 may be associated with unwanted side effects, including patients with heart condition or thyroidectomy following thyroid cancer [19].

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