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Review

Liquid levothyroxine and its potential use

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INTRODUCTION

Levothyroxine (L-T4) is the drug used worldwide in replacement therapy for patients with hypothyroidism, being the third most common medication dispensed in the United States in the last few years.[1] L-T4 is also used as suppressive therapy after surgical removal of thyroid cancer[2] and for treating patients with nodular goiter in order to arrest its growth, although this use is still debated.[3]

L-T4 was first isolated by Kendall in 1914 from animal-derived desiccated thyroid, which contains a combination of T4 and triiodothyronine (T3).[4] Synthetic L-T4 came into use for thyroid treatment in the 1950s and was widely adopted as the primary thyroid hormone replacement drug, replacing the natural desiccated thyroid that had been used during the previous 50-year period.[5]

Traditionally, L-T4 has been available in tablet form as a stable salt that contains sodium; approximately 60-90 % of the dose is absorbed in the jejunum and ileum within 3 hours of ingestion.[6] Absorption is maximal when it is taken on an empty stomach, demonstrating the importance of gastric acidity in the process. In fact, the acid gastric pH is essential to dissolve the tablet, removing sodium ion and converting L-T4 into a lipophilic molecule.[7] Recently, novel formulations of L-T4, such as soft gel capsule and liquid form, have been made available. This review will focus on liquid L-T4 formulation and its potential benefit.

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L-T4 TABLET THERAPY NOT ALWAYS "EASY": CAUSES OF MALABSORPTION

Even though substitutive therapy with levothyroxine has been prescribed for more than 60 years and is considered an "easy" therapy, almost 50% of treated patients show abnormality of thyroid hormone profile after one year of treatment.[8]

There are many reasons to explain this fact. First of all, several conditions and diseases related to the gastrointestinal tract can influence the T4 tablet form pharmacokinetics. Drug dissolution and solubility is altered by an increase in gastric pH: the most common diseases altering the normal acid environment of the stomach are Helicobacter Pylori (HP) related gastritis and atrophic gastritis of the body of the stomach due to hypo/achlorhydria and to the production of ammonia. This mechanism may alter the ionization status and the conformational characteristics of the thyroxine molecule and the efficiency of intestinal absorption of the hormone.[9,10] Centanni et al have clearly demonstrated that patients with impaired acid secretion require an increased dose of thyroxine: the daily requirement of L-T4 was higher (by 22 to 34%) in patients with HP related gastritis, atrophic gastritis or both conditions.[11]

Also the change in pH caused by PPI may be responsible for a reduced absorption of L-T4.[12]

To our knowledge, no data about the duration of the treatment with PPI necessary to inhibit L-T4 absorption is available in the literature. On the other hand, it is known that rapid and consistent pH acid suppression is achieved on the first day of PPI treatment; by this fact, we are led to believe that a few days on PPI treatment may be sufficient to reduce LT4 absorption.[13]

Another condition that requires an increased dose of tablet form L-T4 is celiac disease,[14] including its "atypical" phenotype, characterized by little or no gastrointestinal symptoms. A recent study in celiac patients affected by hypothyroidism due to Hashimoto's thyroiditis showed that if they were not correctly treated with a strict gluten-free diet, the therapeutic dose of T4 had to be increased by at least 50%.[15] Given the prevalence of celiac disease in patients with thyroid autoimmunity (2-5%),[16] it is recommended to always consider the occurrence of an occult gastrointestinal disorder in stable patients on chronic L-T4 therapy who suddenly exhibit a need for an increased dose.

Lactose intolerance can also lead to an increased need for tablet form L-T4.[17]

There are two main reasons for this phenomenon. Undigested lactose draws water into the intestinal lumen and leads to bacterial fermentation; this causes osmosis and accelerates small intestinal transit, which reduces the contact time between lactose and residual enzymes and further decreases the hydrolysis of lactose.[18] Moreover, many L-T4 formulation tablets contain lactose,[19] thus further inducing the disorder with every drug administration.[17] A recent study also found that a strict lactose-free diet in lactose intolerant patients led to a decrease in the TSH level without modifying L-T4 dosage.[20]

It is important to underline that drugs may influence L-T4 absorption.[21]

Last but not least, L-T4 is normally taken with breakfast. It is in well known fact that L-T4 assumption ten minutes before drinking coffee also reduces its absorption (Table 1).[8,21]

Novel formulations of L-T4 and their potential use

Nowadays, novel levothyroxine formulations are available, namely, soft gel capsules and liquid form. The soft gel capsule contains L-T4 dissolved in glycerine in an outer gelatine shell.[22] This structure provides protection from the variations of gastric pH and could also prevent binding to other substances in the intestinal lumen, such as coffee[23] or other medicaments (for example calcium or iron salts).[21,24-27]

The liquid form is composed only of L-T4 of variable concentrations, glycerine and ethanol. The most important advantage of an oral solution, compared to the solid formulation, is the possibility of administration also in patients who are not able to swallow intact capsules or tablets.

Furthermore, as shown in a recent *in vivo* study, liquid L-T4 formulation also has a better absorption

Table 1. Endogenous and exogenous factors interfering with L-T4 absorption

Foods	Gastrointestinal Diseases	Drugs
✓ Food intake	✓ H. pylori infection	✓ Proton Pump Inhibitors
✓ Dietary fiber	✓ Lactose intolerance	✓ Ferrous sulfate
✓ Coffee	✓ Celiac Disease	✓ Calcium carbonate
✓ Pompelmo Juice	✓ Jejunoileal bypass or other bowel resection	✓ Sucralfate
✓ Soya	✓ Inflammatory Bowel Disease	✓ Sevelamer and other phosphate binders (e.g. Lanthanum carbonate)
	✓ Chronic Autoimmune Gastritis	✓ Cholestyramine
	✓ Biliary cirrhosis	✓ Ciprofloxacin
		✓ Raloxifene
		✓ Aluminium hydroxide
		✓ Orlistat

rate. In fact, Yue et al have shown that L-T4 in liquid formulation peaks in blood faster than the tablet or the soft gel capsule (faster at maximum concentration (ng/mL) by an average of 30 min).[28] The levothyroxine rate and the extent of exposure are similar in the three types of formulations (tablets, soft gel capsule and liquid form), but the solution appears to reach the systemic circulation faster as dissolution is not needed before absorption starts.

These pharmacokinetic features could be responsible for lower drug-food interactions.

PROTON PUMP INHIBITOR AND LEVOTHYROXINE TREATMENT

Because both LT4 and PPI are top prescribed drugs worldwide, it is not uncommon to encounter patients who take them concurrently.[12] By inhibiting the H+/K+ ATPase pump in the gastric parietal cells, PPIs increase gastric pH and therefore impair tablet LT4 dissolution that occurs in the acid environment of the stomach, thereby reducing its absorption. When LT4 therapy fails to reach target serum TSH values, this is often addressed by increasing the daily dose of LT4. However, should the physician withdraw the interfering drug (or should the patient elect to do so) while maintaining the increased LT4 dose, there is then a real risk of iatrogenic hyperthyroidism. This situation is similar to LT4 over treatment occurring postpartum if the LT4 dose has not been decreased back to the pre-pregnancy dose. LT4 over treatment is particularly undesirable in older patients, in whom the risk of arrhythmias or fracture is higher.[29] In addition, the necessity of monitoring serum TSH regularly causes serum TSH assays to be repeated frequently, a practice that raises health costs.

Recent studies by Vita R et al have clearly demonstrated that tablet LT4 malabsorption induced by PPI are resolved effectively with both the soft gel capsule and the liquid solution.[31,32]

"GOOD BREAKFAST FOR A GOOD MORNING"

Coffee impairs tablet L-T4 absorption by binding L-T4.[23] Furthermore, studies on stability, carried out with tablet formulations, have shown that sodium L-T4 is rapidly degraded at 60° C.[33,34] In a well researched study, Bernareggi et al performed *in vitro* recovery tests on known concentrations of T4 in the presence of saline, freshly brewed espresso coffee or known T4 sequestrants such as dietary fibers from bran or drugs like sucralfate.[23] While in saline T4 recovery was complete, after dilution of T4 solution in coffee it ranged from 56 to 80%. The T4 recovery was even lower in suspensions of dietary fibers and sucralfate (ranging from 17% to 47%). These findings may be due to T4 sequestration or T4 degradation. Conversely, stability of levothyroxine liquid formulation in milk, tea, coffee with milk warmed to 50° C and orange juice at room temperature was demonstrated at up to 20 minutes of incubation, without evidence of T4 degradation in different types of matrices.[35]

Recently, Cappelli *et al*. highlighted the same results in a small group of 54 patients who wrongly consumed oral liquid L-T4 prior to breakfast within the very first few minutes or also at breakfast in their coffee. A comparable thyroid hormonal profile was obtained in patients who wrongly took L-T4 liquid formulation compared to controls who consumed it 30 min before breakfast.[36]

The hypothesis is that the presence of alcohol in the liquid formulation could play a key role in the absorption of T4. Indeed, oral mucosal drug delivery is known as an alternative method for systematic drug delivery offering several advantages.[37] Because the oral mucosa is highly vascularized, drugs that are absorbed through the oral mucosa enter the systemic circulation directly, bypassing the gastrointestinal tract.[37] Furthermore, it is conceivable that liquid L-T4 formulation could also be better absorbed because it circumvents the pH related dissolution phase.

L-T4 THERAPY AFTER BARIATRIC SURGERY

These considerations are also useful in patients who undergo bariatric surgery.

Usually, once ingested, only a small fraction of levothyroxine tablet form is assimilated in the stomach, being mainly absorbed in the small intestine, in particular in the duodenum and jejunum;[6] this fact explains why patients suffering from short bowel syndrome (following bowel resection) require a higher dosage of levothyroxine.[38,39] The liquid L-T4

formulation may minimize this problem. In fact, a recent study has shown a reversible normalization of serum TSH levels in patients submitted to bariatric surgery (in particular to Roux-en-Y gastric bypass), after switching from the tablet form of L-T4 to oral liquid formulation. The observation that the switch from a tablet to oral formulation was effective in normalizing serum TSH levels and that switching back to the tablet formulation led to an increase of TSH levels in our patients after bariatric surgery leads us to believe that the absorption of T4 is greater when an oral liquid formulation is used.[40] Furthermore, it is conceivable that liquid L-T4 formulations could also circumvent the pH alteration resulting from a gastric bypass.

L-T4 AND ENTERAL NUTRITION

Working on the basis of the possible amelioration of liquid L-T4 therapy also on a non-empty stomach, we recently analyzed the thyroid hormonal profile in patients with an enteral feeding tube after total laryngectomy for laryngeal cancers. Since total thyroidectomy is a common surgical practice in patients submitted to this kind of surgery,[41] these patients also started L-T4 replacement therapy after surgery. The majority of clinicians suggest that enteral feedings should be carried out 1-2 hours prior to and after L-T4 administration despite the lack of data supporting continuous enteral nutrition.[42] We compared the thyroid hormonal profile in 20 patients submitted to L-T4 treatment in tablets or in liquid formulation with an enteral feeding tube and we found no difference of TSH, fT4 and fT3 between patients treated with tablets interrupting enteral continuous nutrition for 30 min before and after L-T4 administration and patients treated with liquid formulation placed into the nasoenteric tube immediately. Furthermore, the nurses preferred the use of liquid formulations to crushed tablets, since it reduced the time spent preparing and administering the medication. Moreover, crushing tablets before administering them may change and alter the pharmacokinetics and pharmacological properties.[43] Our data showed that liquid L-T4 formulation can be administered through a feeding tube with no need for an empty stomach.[44] These data reinforces our hypothesis that oral L-T4 liquid formulation could be very helpful in coping with the problem of L-T4 malabsorption caused by food when using traditional tablet formulations, as has also been recently demonstrated both in adults and in children.[45,46]

LIQUID FORMULATION IN PAEDIATRIC PATIENTS

Giving levothyroxine to infants can be a challenge when it is prescribed in tablet form which often needs to be crushed. Use of liquid L-T4 formulation has been investigated for the first time in paediatric patients with congenital hypothyroidism. This is the most frequent congenital endocrine disorder and early treatment enables normal mental and physical development. However, some children, despite early diagnosis and therapy, show abnormal mental development and poor long-term outcome. There are many reasons for this phenomenon such as the age at the start of the therapy, socio-economic factors, the parents' compliance and the initial dosage of L-thyroxine.[47] An initial daily dose of 10-15 mcg/kg, according to prenatal severity of congenital hypothyroidism, has been recommended in the US and Europe.[48,49]

Peroni et al compared L-T4 liquid and tablet formulations in the initial treatment of congenital hypothyroidism, demonstrating that normalization of TSH is achieved in significantly more patients taking the liquid formulation than those on the tablet formulation; moreover, infants in treatment with liquid formulation had significantly lower TSH values.[46] Cassio et al also showed an incomplete bioequivalence between drops and tablets. L-T4 liquid formulation normalized TSH in significantly more patients affected by severe congenital hypothyroidism; no significant differences were reported in patients with moderate/mild hypothyroidism.[50]

BETTER STABILITY OF LIQUID FORMULATION

Several studies have compared the effectiveness of liquid L-T4 formulation over tablet form in keeping the patient euthyroid. Negro *et al*. demonstrated that liquid formulation, as compared to the tablet, resulted in a significantly higher number of hypothyroid patients who maintained the euthyroid state in 12 months of follow-up, with a significant reduction of variability in TSH values.[51] Our recent retrospec-

tive study confirms and extends this data. In fact, we found a greater stability of thyroid hormonal profile in a group of 118 hypothyroid elderly patients (≥65 years old) in replacement therapy with liquid L-T4 compared to 299 patients treated with L-T4 in tablet form. In particular, subclinical or hyperthyroidism is significantly lower in our patients treated with liquid L-T4 than those taking tablets over five years of replacement therapy.[52]

Despite the wide use of levothyroxine, it has been shown that up to 40% of patients are over-treated, thus developing subclinical hyperthyroidism.[53,54] This is of particular concern in older patients (≥65 years old) due to the well-documented increased risk of developing heart disease, osteoporosis, bone fractures and cognitive impairment.[55-57] In a recent review, Biondi recommended treating sub-clinical hyperthyroidism in elderly patients because of the increased risk of atrial fibrillation, osteoporosis and bone fractures and the higher risk of progression to overt disease.[55] Moreover, Collet et al have clearly demonstrated with 52,647 participants that sub-clinical hyperthyroidism is also associated with an increased risk of total coronary heart disease mortality.[56] Cognitive aspects also do not seem to be immune to low values of serum thyreotropin. In fact, Moon JH et al have recently shown that low TSH levels are associated with the development or progression of cognitive impairment, including dementia, in the elderly.[57] For all these reasons, prolonged TSH stability in patients in substitutive L-T4 treatment is mandatory.

LIQUID FORMULATION IN SUPPRESSIVE THERAPY FOR THYROID CANCER

The tolerability and efficacy of liquid L-T4 vs. the previous tablet formulation was evaluated in a cohort of 59 patients with cured differentiated thyroid cancer (DTC). The modality of L-T4 administration proved adequate in both tablet and liquid formulation in 64% and 68%, respectively, of patients who fully complied with the protocol. At the end of the protocol, 73% of patients requested to remain on the liquid formulation.[58] No change in TSH, thyroid hormones or thyroglobulin was noted during the study.

CONCLUSION

Many studies suggest for the first time that liquid L-T4 formulation could reduce the problem of L-T4 malabsorption encountered when using traditional tablet formulations. This could ameliorate the compliance of 'thyroid' patients, while simultaneously reducing health expenditure. The potential use of new L-T4 forms in a wide range of malabsorption conditions makes this formulation very attractive for both physicians and patients.

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