Endocrinología, Diabetes y Nutrición 71 (2024) 93–95

Endocrinología, Diabetes y Nutrición

www.elsevier.es/endo

EDITORIAL

New formulations of levothyroxine in the treatment of hypothyroidism

Nuevas formulaciones de levotiroxina en el tratamiento del hipotiroidismo

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Hypothyroidism is one of the main endocrine disorders. It usually develops as a result of chronic autoimmune thyroiditis, thyroid surgery, or radioiodine treatment. Its global prevalence is between 3.8–11.7% of the population,[1,2] with the majority being subclinical forms. This condition is more common in women, and its frequency increases with age. It is estimated that with the increase in life expectancy, the prevalence of hypothyroidism will continue to increase in the future. Due to its high prevalence and the need for long-term treatment, levothyroxine (LT4) has become one of the most prescribed drugs today.[3]

LT4 is the synthetic form of the hormone thyroxine secreted by the thyroid gland. The most frequently used pharmaceutical form is the tablet. The effectiveness of LT4 can be affected by several factors, such as treatment adherence problems or nutritional, pharmacological and pathological factors.[4] Absorption of LT4 is optimal when taken on an empty stomach, reaching its maximum in 1.5—2 h. However, absorption may be decreased and delayed if the tablets are taken with breakfast or foods rich in fibre, grapefruit juice, coffee, milk or supplements containing calcium, iron, fibre or soya. Therefore, taking the LT4 tablet on an empty stomach and waiting at least 30 min before consuming foods or products that may affect its absorption is recommended.

Both branded and generic LT4 tablets may have different dissolution profiles in relation to gastric pH, which proves that the excipients and manufacturing techniques used can influence the absorption of LT4. Furthermore, several medications can interfere with the absorption of LT4 through different mechanisms, such as the modification of gastric pH (proton pump inhibitors, H_2 antagonists and other antacids), the formation of insoluble precipitates (iron and calcium salts, and bile acid sequestrants) and the alteration of LT4 transporters in the intestinal mucosa (ciprofloxacin and rifampin).[5]

Finally, for adequate absorption of LT4, it is necessary to have an intact gastrointestinal mucosa epithelium. Several diseases, such as *Helicobacter pylori* infection, chronic atrophic gastritis, coeliac disease, lactose intolerance, intestinal parasites, jejunoileal bypass, intestinal resection, inflammatory bowel disease and pancreatic insufficiency, can negatively affect the bioavailability of LT4 tablets.[4]

The dose of LT4 used in treating hypothyroidism depends on several factors, including body mass index, the patient's age, the underlying cause of the hypothyroidism, and the amount of residual thyroid tissue after thyroid surgery. The initial dose varies between 1.6 and 1.8 μg/kg/day and is modified based on thyrotropin (TSH) at 6–8 weeks to maintain its levels within the normal range. Hypothyroidism is considered refractory when a dose greater than 1.9 μg/kg/day is required to achieve a normal TSH level.[5]

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The clinical consequences of inadequate hormone replacement therapy can be significant from both a clinical and health perspective. An excessive dose of LT4 is associated with subclinical or frank thyrotoxicosis. When the dose is insufficient, the patient may experience persistent symptoms of hypothyroidism. Inappropriate TSH elevation is managed by increasing the daily dose of LT4 with reassessment of TSH at 2–6 months. However, increasing the dose of LT4 can lead to iatrogenic thyrotoxicosis, especially when underlying disorders have been corrected, such as following a gluten-free diet in the case of coeliac disease or discontinuing drugs that interfere with LT4 absorption. A recent retrospective study conducted in 14,533 individuals in whom LT4 was initiated showed a cumulative risk of over-treatment (TSH < 0.1 μU/mL) or under-treatment (TSH > 10 μU/mL) of 4.7 and 7.4%, respectively, after 10 years.[6] Finally, inappropriate hormone replacement therapy places a greater burden on both the patient and the healthcare system in terms of additional medical visits, frequent laboratory tests, and the need to continually adjust the LT4 dose.

To avoid the inconveniences associated with tablets, adapt to patients with problems swallowing them, and address the need to find an optimal treatment not affected by drug interaction and gastrointestinal malabsorption, new formulations of Oral LT4, such as the liquid formulation and soft gelatin capsules have been designed.

Since January 2022, the liquid formulation of LT4 has been available in our country. This presentation consists of a transparent, colourless solution supplied in opaque white 1 mL single-dose containers, without any type of excipients. The formulation comprises LT4 sodium, with doses ranging from 13 to 200 μg, and glycerol at 85%.

Liquid LT4 has certain advantages over tablets, supported by several studies that have shown a higher absorption rate of LT4, a maximum concentration in the blood in a shorter time, and lower and more stable levels of TSH.[7,8]

Although the SmPC does not specify it, liquid formulations of LT4 offer the advantage of allowing patients with hypothyroidism to take their medication with meals or coffee, avoiding the currently recommended waiting period of 30–60 min, facilitating therapeutic compliance. This possibility has been confirmed in several studies that found no significant differences in serum levels of TSH, free thyroxine or free triiodothyronine between the liquid LT4 solution, with or without waiting periods before breakfast, coffee consumption or a meal rich in fats.[9,10]

The liquid formulation of LT4 is absorbed better than tablets in clinical situations involving malabsorption.[11] Some studies have shown that proton pump inhibitors do not significantly interfere with the absorption of LT4 when administered in liquid form.[12] The interference of ferrous sulphate or calcium carbonate is lower with the solution than with the LT4 tablet.[13] In newly diagnosed hypothyroid subjects with *Helicobacter pylori* infection, it has been observed that the administration of LT4 in liquid form can generate a more favourable clinical response compared to tablets.[14]

Other potential benefits of the liquid formulation include its compatibility with milk for use in infants with congenital hypothyroidism, its ease of administration in paediatric patients with difficulty swallowing tablets, its ability to be administered through feeding tubes in patients with enteral nutrition, and in cases of myxoedema coma when intravenous LT4 is not available.[5]

In our country, the liquid formulation of LT4 has its drawbacks: cost (about 7 times more expensive than tablets) and lack of financing at the moment. For example, for a daily prescription of 100 μg, the monthly price of liquid LT4 would be €10.9 compared to €1.5 for tablets. Another drawback would be the discomfort involved in its administration, as it requires opening a single-dose container, pouring the contents into a glass of water, in the mouth or on a spoon, and ingesting it immediately.

Another formulation of oral LT4 not yet marketed in Spain is the soft gelatin capsule. In this case, LT4 is dissolved in glycerine and then encapsulated with a soft gelatin shell in the form of a translucent flat oval capsule. Its absorption is faster than that of tablets and does not depend on gastric pH. The bioequivalence between the tablets and the soft gelatin capsule has been confirmed in healthy volunteers.[15] This new oral formulation also helps avoid the decrease in bioavailability of LT4 tablets caused by pharmacological interference and concomitant diseases related to malabsorption, improving therapeutic efficacy.[5] Compared to liquid LT4, the capsules are easier to take, and the container is smaller and easier to transport.

At present, other routes of administration of LT4 are being evaluated, such as intranasal, sublingual, intramuscular, intrarectal, transdermal and aerosol. Likewise, nanomaterials are being explored to develop administration systems that allow the sustained release of LT4 to improve patient comfort and reduce the costs associated with treatment.[5]

In conclusion, administration of LT4 in tablet form is an effective treatment for most patients with hypothyroidism. However, new formulations of oral LT4, such as liquid T4 and soft gelatin capsules, can be a good therapeutic alternative in cases of low adherence to treatment due to recommended fasting, difficulties swallowing tablets, gastrointestinal surgery, patients wearing an enteral nutrition tube, drug interactions, gastrointestinal disorders that cause malabsorption, and poor and unexplained biochemical control of hypothyroidism.

References

1. Garmendia Madariaga A, Santos Palacios S, Guillén-Grima F, Galofré JC. The incidence and prevalence of thyroid dysfunction in Europe: A meta-analysis. J Clin Endocrinol Metab. 2014;99:923–31.
2. Wyne KL, Nair L, Schneiderman CP, Pinsky B, Antunez Flores O, Guo D, et al. Hypothyroidism prevalence in the United States: A retrospective study combining National Health and Nutrition Examination Survey and claims data, 2009-2019. J Endocr Soc. 2022;7:bvac172.
3. The Top 200 of 2020 [Internet]. [Accessed 14 October 2023]. Available from: https://clincalc.com/DrugStats/Top200Drugs.aspx.
4. Virili C, Antonelli A, Santaguida MG, Benvenga S, Centanni M. Gastrointestinal malabsorption of thyroxine. Endocr Rev. 2019;40:118–36.
5. Liu H, Li W, Zhang W, Sun S, Chen C. Levothyroxine: Conventional and novel drug delivery formulations. Endocr Rev. 2023;44:393–416.

6. la Cour JL, Medici BR, Grand MK, Nicolaisdottir DR, Lind B, Faber J, et al. Risk of over- and under- treatment with levothyroxine in primary care in Copenhagen, Denmark. Eur J Endocrinol. 2021;185:673–9.
7. Yue CS, Scarsi C, Ducharme MP. Pharmacokinetics and potential advantages of a new oral solution of levothyroxine vs. other available dosage forms. Arzneimittelforschung. 2012;62: 631–6.
8. Fallahi P, Ferrari SM, Antonelli A. Oral L-thyroxine liquid versus tablet in patients with hypothyroidism without malabsorption: A prospective study. Endocrine. 2016; 52:597–601.
9. Cappelli C, Pirola I, Daffini L, Formenti A, Iacobello C, Cristiano A, et al. A double-blind placebo-controlled trial of liquid thyroxine ingested at breakfast: Results of the TICO study. Thyroid. 2016;26:197–202.
10. Ducharme M, Scarsi C, Bettazzi E, Mautone G, Lewis Y, Celi FS. A novel levothyroxine solution results in similar bioavailability whether taken 30 or just 15 minutes before a high-fat high-calorie meal. Thyroid. 2022;32:897–904.
11. Fallahi P, Ferrari SM, Elia G, Ragusa F, Paparo SR, Antonelli A. L-T4 therapy in enteric malabsorptive disorders. Front Endocrinol. 2021;12:626371.
12. Vita R, Saraceno G, Trimarchi F, Benvenga S. Switching levothyroxine from the tablet to the oral solution formulation corrects the impaired absorption of levothyroxine induced by proton-pump inhibitors. J Clin Endocrinol Metab. 2014;99:4481–6.
13. Benvenga S, Di Bari F, Vita R. Undertreated hypothyroidism due to calcium or iron supplementation corrected by oral liquid levothyroxine. Endocrine. 2017;56:138–45.
14. Ribichini D, Fiorini G, Repaci A, Castelli V, Gatta L, Vaira D, et al. Tablet and oral liquid L-thyroxine formulation in the treatment of naïve hypothyroid patients with Helicobacter pylori infection. Endocrine. 2017;57:394–401.
15. Colucci P, D'Angelo P, Mautone G, Scarsi C, Ducharme MP. Pharmacokinetic equivalence of a levothyroxine sodium soft capsule manufactured using the new food and drug administration potency guidelines in healthy volunteers under fasting conditions. Ther Drug Monit. 2011;33:355–61.