Editorial

Reassessment of combined LT4 and LT3 treatment for hypothyroidism: the prospects for slow-release T3 preparations

Leonidas H. Duntas

Endocrine Unit, Evgenidion Hospital, Athens University Medical School, Athens, 115 27, Greece

"Τῶν δ'ως λόγου μόνου ξυμπεραινομένων μή είη έπαύρασθαι, τῶν δε ως έργου ενδείξιος"
"Do not draw conclusions which arise from logic alone, but also from practical demonstration"
Hippocrates

The introduction of synthetic levothyroxine (LT4) in the late 60's for treatment of hypothyroidism radically changed the therapeutic approach for patients with thyroid failure, enabling a more physiologic, dose-related treatment. Subsequently, the availability of LT4 preparations at a variety of doses led to an even more precise and individualized treatment schedule. Concomitantly, the acquired knowledge that T4 is converted peripherally to T3, which is much more strongly bound to thyroid hormone receptor than T4, has established the use of the LT4 as the treatment of choice for hypothyroidism[1,2]. Further studies revealing T4's long half-life of 7 days in contrast to the short 1-day half life of T3, as well as the constancy of T4 levels after oral administration, facilitated titration of its dose and have decisively contributed to its increasing utilization worldwide over the last 30 years[3,4]. It has been established that orally or injected T3 disappears from the circulation at a much faster rate than T4, mainly owing to lesser affinity of the serum binding proteins for T3. At times T3 has been added at various dosages or as a fixed preparation, containing T4 and T3 in various ratios (T4:T3 of 1:5 or 1:10), this regimen however has not been established as the treatment of choice for thyroid failure[5]. This is mostly due to the several side effects of T3, such as tachycardia and nervousness, which may severely affect compliance.

In 1999, a report by Bunevicius et al. provided evidence that combined treatment with T4 and T3 was of benefit in the treatment of hypothyroidism, especially improving quality of life.[6] Nevertheless, this study has been met with scepticism and criticism based primarily on the methods and conclusions of the investigation. In the meantime, four reports and at least three editorials have justified the criticism of Bunevicius' study since no other results could demonstrate any benefit of the combined treatment in hypothyroidism[7-12]. This series of investigations has been extended with the enquiry by Fadeyev et al. in this issue of *Hormones*[13]. In a randomised non-placebo controlled study, the authors evaluated the parameters of thyroid function in patients with primary hypothyroidism treated with LT4

Address correspondence and requests for reprints to:
Leonidas H. Duntas, M.D., Endocrine Unit, Evgenidion Hospital, University of Athens, 20 Papadiamantopoulou Str., 11528 Athens, Greece, e-mail: ledunt@otenet.gr
Received 16-03-05, Accepted 30-03-05

alone or in combination with LT4 and LT3. They found FT4 levels in patients under monotherapy to be higher than in controls. These results are in accordance with those of other studies using combined treatment[8-10]. In a recent study designed to examine whether or not the combined treatment with T4/T3 (absorbed molar ratio 14:1) is of advantage over T4 alone as regards mood and cognition, no difference between the two regimens[14] was disclosed. Moreover, combined treatment with T4 plus T3 did not show any advantage compared with the standard treatment with T4 alone in infants with congenital hypothyroidism[15]. Although in all these studies various combinations of T3 to T4 have been applied, the T3 was administered as a bolus once or twice daily, which, due to its pharmacokinetics, cannot simulate the physiologic constancy of extra thyroidal T3 production which leads to normal serum T3 levels. Therefore, the main criticism of all these studies is that the use of T3 as scheduled cannot mimic the physiologic molar ratio of T4/T3[5]. Moreover, this schedule may generate problems regarding patient's compliance.

A very recent randomized trial evaluated the combination of LT4 plus LT3 in 28 hypothyroid patients at a dosage which may reflect the proportions of secretions of the human thyroid gland. The add-on combination with LT4 87.5 μg/day plus LT3 7.5 μg/g led to increased LT3 and decreased TSH levels compared with standard treatment[16]. These results also suggested that combination treatment with LT4 plus LT3, even at a physiologic dosage, does not offer any concrete advantage when compared with standard therapy. However, in this study 40% of the patients preferred the combination treatment mentioning that they simply felt better[16]. This therefore shows a discrepancy between theoritical expectations and the real data.

Over the past few years the aim has been to produce LT3 preparations in a slowly absorbed, time-released formulation[17]. The application of such a formula was recently reported by Hennemann at al[18]. The authors convincingly demonstrated that the use of a new slow-release formulation of LT3 at a low dose combined with LT4 in treating hypothyroid subjects led to considerable increase of serum T4 and T3 levels and improvement of the T4/T3 ratio and serum TSH as compared to monotherapy[18]. They could not detect any serum peak of T3 in contrast to administration of plain T3. Although the authors did not give any details of the chemical nature of the new compound, it undoubtedly represents an important development that needs to be further evaluated in future studies. The introduction of a slow-release compound of this nature promises to enrich the arsenal of thyroid hormone preparations, thus enhancing management of situations like euthyroid sick syndrome, certain cases of depression and subclinical hypothyroidism[19,20].

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