HOW DO YOU DECIDE WHAT DOSE OF THYROXINE IS APPROPRIATE FOR A PATIENT WITH SECONDARY HYPOTHYROIDISM?

Koulouri O, Auldin MA, Agarwal R, Kieffer V, Robertson C, Smith JF, Levy MJ, Howlett TA. **Diagnosis and treatment of hypothyroidism in TSH deficiency compared to primary thyroid disease: pituitary patients are at risk of under-replacement with levothyroxine.** Clin Endocrinol. 2011 [Epub ahead of print]. doi: 10.1111/j.1365-2265.2011.03984.x.

SUMMARY

BACKGROUND

Pituitary tumors can destroy thyrotrophs or disrupt their function, causing secondary hypothyroidism as well as affecting other endocrine axes. The treatment of pituitary tumors can further disrupt endocrine axes, producing effects that may be permanent or temporary. What is more, replacing thyroid hormone can exacerbate adrenal insufficiency, and replacing growth hormone can affect the thyroid axis (1).

METHODS

The authors assessed how effective they had been in titrating the levothyroxine (L-T_4) dose empirically to "keep the free T_4 in the middle to upper part of the normal range" in 514 patients with secondary hypothyroidism associated with pituitary tumors. The patients had a wide variety of pituitary tumors and therapies, had been followed for up to 10 years, and had last been seen between 2007 and May 2009. Information on tumor size, history of surgery/radiotherapy, and data on pituitary hormone and L-T_4 replacement were retrieved, as were the most recent free T_4 and thyrotropin (TSH) values. Patients were divided into those with "low-risk" adenomas, who were at any stage of management as long as they had had no surgery or radiotherapy, and those with "high-risk" macro lesions and/or surgery or radiotherapy. A total of 16 of the 171 low-risk patients were receiving L-T_4, and 131 of 343 high-risk patients were receiving L-T_4. The authors compared the free T_4 levels obtained in these patients with free T_4 levels in some interesting control groups: (1) patients with treated primary hypothyroidism, (2) patients who formerly had been thyrotoxic but now were euthyroid without receiving either L-T_4 or carbimazole, or (3) patients who formerly had been thyrotoxic and now were euthyroid while taking L-T_4. All controls had to have a free T_4 in the normal range (9 to 25 pmol/L) and a normal TSH (0.3 to 5.0 mIU/L).

RESULTS

No free T_4 below the normal range was observed in patients who had not been prescribed L-T_4. However, 17% of the high-risk group who were not taking L-T_4 did have a free T_4 at or below 11 pmol/L, as compared with 8.4% of the control patients who formerly were thyrotoxic and now were euthyroid on no treatment ($P<0.0001$). In high-risk patients for whom L-T_4 had been prescribed, 3.8% had a free T_4 below the lower limit of normal (9 pmol/L). Furthermore, 38% had free T_4 at or below 13 pmol/L, a significantly larger proportion than the 9.5% of the controls who formerly were thyrotoxic and the 13.4% of the patients with primary hypothyroidism for whom L-T_4 had been prescribed ($P<0.0001$ for both). On the other hand, if the authors had succeeded in obtaining a free T_4 level above 15 to 16 pmol/L in their patients, they would have exceeded the levels found in one third to one half of patients with primary hypothyroidism, suggesting that if they had achieved their aim, some patients with pituitary tumors and hypothyroidism would have been over-replaced.

CONCLUSION

Trying to keep the free T_4 in the middle to upper part of the normal range by empirically titrating the L-T_4 dose left a substantial fraction of patients with pituitary tumor under-replaced, when compared with the free T_4 levels found in controls with primary thyroid disease who were euthyroid.

COMMENTARY

Once the possibility of adrenal insufficiency is addressed, a patient with a pituitary tumor who has a low or low-normal free T_4 is generally given L-T_4, but how much should be given? TSH levels cannot be used as a monitor in secondary hypothyroidism: they may be low, more commonly are inappropriately normal, and may even be slightly above normal. True, when L-T_4 is given, the TSH level will fall further, but when the correct replacement dose is reached, the TSH will be suppressed, often becoming undetectable. On the other hand, aiming for a dose that results in a free T_4 level in the middle to upper range of normal is not patient-specific: the normal reference range is based on a population-average whereas normal individuals control their free T_4 much more closely (2).

One suggested alternative approach is to give all patients under 60 years of age at least a blanket dose of L-T_4 at 1.3 µg/kg of body weight (3). However the L-T_4 replacement dose in primary hypothyroidism can vary more than threefold between individuals: one size does not fit all.

Clinicians know they must watch for chronic over-replacement in treating primary hypothyroidism to avoid osteoporosis and cardiac arrhythmias, while watching for chronic under-replacement to avoid cardiovascular risks. Unfortunately, the risks of over-replacement or under-replacement are more grave in patients who have undergone pituitary surgery—not only during the postoperative period but over the long term—as they have a substantially increased long-term mortality, primarily reflecting vascular death. (The current study did not assess thyroid hormone levels in those pituitary patients who might have died before 2007.) The increase in mortality is true even when patients with a history of Cushing's disease or acromegaly are excluded (4). The standardized mortality ratio is higher in women than in men, and it is even higher in younger patients, although some of this mortality may reflect cerebrovascular problems secondary to radiotherapy for craniopharyngioma (4).

Although a number of thyroxine-responsive gene products have been considered as surrogates for the TSH level, thus far none has proven to be very useful clinically. Perhaps they could be combined along with some physiological parameters to come up with a more satisfactory approach to the hazards of establishing the proper replacement dose of L-T_4 for each individual patient with secondary hypothyroidism.

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References

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