Propranolol-Induced Hyperthyroxinemia in a Patient With an Autonomous Thyroid Nodule

N. David Charkes, MD, and Edward B. Polin, MD
Philadelphia, Pennsylvania

Recent studies have shown that about one out of every five euthyroid persons with an autonomous thyroid nodule will become hyperthyroid during the next six years, often going through a phase of triiodothyronine (T_3) thyrotoxicosis first.[1] Propranolol is commonly used to control some of the symptoms of the developing hyperthyroid state. Having had the opportunity to follow such a patient, however, it was found that the progressive increase in serum thyroxine (T_4) concentration and free thyroxine index (FT_4I) into the hyperthyroid range was the result of the propranolol treatment, not of hyperthyroidism from the nodule, ie, the drug had produced so-called "euthyroid hyperthyroxinemia"[2] in the patient. Thus the treatment mimicked the natural history of the disease.

CASE REPORT

A.J., a 42-year-old unmarried woman, was first seen in 1977 because of nervousness, an 8-lb weight loss, insomnia, palpitations, heat intolerance, increased sweating, tremulousness, and loose, frequent bowel movements, all of which had developed over the preceding two to three months. The patient's sister was being treated for an overactive thyroid gland. On examination the woman appeared to be nervous, with a pulse rate of 90 beats per minute; no tremor was present. The thyroid gland was normal in size, but the left lobe felt rounded. The clinical picture suggested hyperthyroidism, but serum concentrations of T_4 and T_3 by radioimmunoassay (RIA) were within the normal range, T_4 151 nmol/L (11.7 μg/dL) and T_3 1.8 nmol/L (114 μg/dL).* Radioiodine uptake was 0.06 (6 percent) in two hours and 0.19 (19 percent) in 24 hours. A thyroid scintigram (iodine 123) confirmed the normal size of the gland, showing a functioning nodule in the left lobe (Figure 1). This nodule was not suppressed after liothyronine administration, 25 μg every eight hours for three days, but there was a marked decrease in ^{123}I uptake elsewhere in the gland. These findings are diagnostic of an autonomous nodule with euthyroidism,[3] and they confirm the normal blood hormone determinations. The patient's symptoms were thought to be the result of anxiety neurosis and depression. She was treated with reassurance, and told to take diazepam, 5 mg as needed, and nortriptyline, 25 mg once daily, but symptoms persisted.

Three years later serum T_3 had become minimally elevated at 3.5 nmol/L (225 μg/dL) despite a persistently normal T_4 value of 142 nmol/L (11.0 μg/dL) and a resin uptake of 0.86 (86 percent), which suggested a developing T_3 toxicosis.[1] Propranolol was subsequently started, 10 mg four times a day, with symptomatic improvement. Two weeks after starting propranolol, serum T_3 had returned to the normal range of 2.8 nmol/L (182 ng/dL), and serum T_4 rose to 166 nmol/L (12.9 μg/dL) with a resin uptake of 1.02 (102 percent). At five weeks serum T_4 was in the hyperthyroid range at 190 nmol/L (14.8 μg/dL), and serum T_3 had fallen further to 2.6 nmol/L (169 ng/dL) with a resin uptake of 0.96 (96 percent). Thyroid scintigram at this time showed no change from the baseline study done three years previously, and a thyrotropin-releasing hormone (TRH) test gave a normal response, indicative of euthyroidism (serum thyroid-stimulating hormone [TSH] 2.0 mU/L baseline; 10.0 mU/L 30 minutes after intravenous administration of 500 μg of TRH) (2.0 μg/mL baseline; 10.0 μg/mL 30 minutes after intravenous administration of 500 μg of TRH). Propranolol treatment was continued, but symptoms persisted, including a 6-lb weight loss over a three-month period despite an increased appetite.

One year after starting propranolol, serum T_4 remained elevated at 190 nmol/L (14.8 μg/dL) with resin uptake at 0.93 (93 percent). At this point the drug was abruptly discontinued. Three weeks later serum T_4 had returned

* *Normal values for laboratory: serum T_4 58 to 167 nmol/L (4.5 to 13.0 μg/dL); serum T_3 1.2 to 3.4 nmol/L (80 to 220 ng/dL); serum TSH 0.0 to 5.5 mU/L (0.0 to 5.5 μU/mL); T_3 resin uptake 0.86 to 1.14 (86 to 114 percent).*

Submitted, revised, April 3, 1987.

From the Departments of Diagnostic Imaging and Medicine, Temple University Medical School, Philadelphia, Pennsylvania. Requests for reprints should be addressed to Dr. N. David Charkes, Section of Nuclear Medicine, Temple University Hospital, Philadelphia, PA 19140.

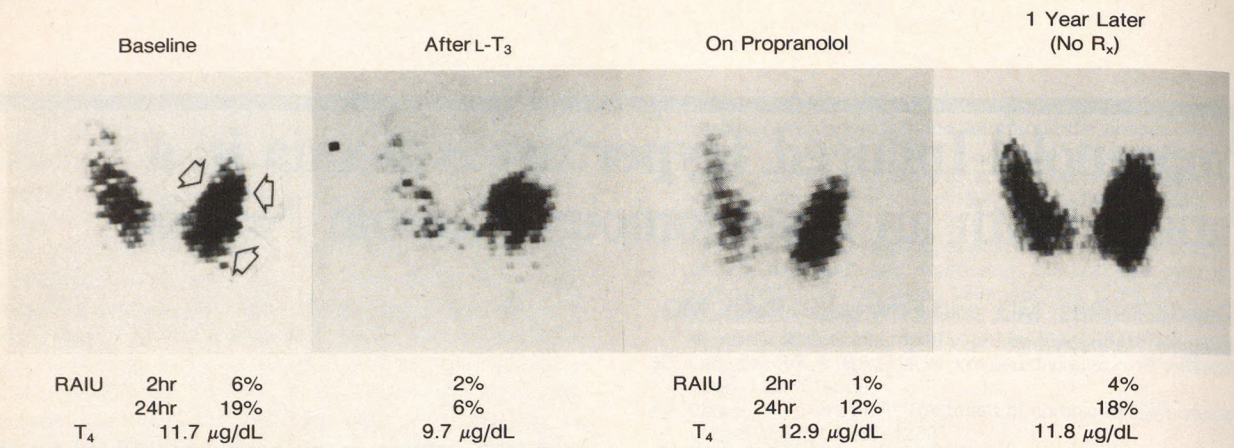

Figure 1. Baseline thyroid scintigram (iodine 123) shows functioning nodule in left lobe (arrows), not suppressed by triiodothyronine (L-T_3) and therefore autonomous.[3] Note suppression of extranodular tissue, indicative of euthyroidism. While on propranolol, serum T_4 has risen but scan is unchanged. One year later, after stopping propranolol therapy, scan is again similar to baseline

to the normal range at 152 nmol/L (11.8 μg/dL) with resin uptake at 1.00 (100 percent) and a TRH test again gave a normal response, albeit somewhat lower than the response when the patient was taking propranolol (serum TSH 2.6 mU/L baseline; 5.2 mU/L 30 minutes after 500 μg of TRH given intravenously) (serum TSH 2.6 μg/mL baseline; 5.2 μg/mL 30 minutes after 500 μg of TRH given intravenously). A repeat thyroid scintigram was similar to the baseline study. The patient remains off propranolol and continues to have the same complaints; serum T_4 has remained within the normal range at 144 nmol/L (11.2 μg/dL) with resin uptake at 0.91 (91 percent).

DISCUSSION

Monodeiodination of thyroxine (T_4) to triiodothyronine (T_3), chiefly within the liver and kidneys, is an important degradative pathway in thyroid hormone metabolism, accounting for over 80 percent of the circulating T_3 present in the blood of healthy individuals.[4] Free (unbound) T_3 diffuses into the body cells and exerts a controlling influence on protein synthesis and respiration through binding to nuclear and mitochondrial receptors. In rat pituitary glands, however, about one half of the T_3 available to thyrotrophs is generated intracellularly from T_4.[5] Propranolol is one of a number of drugs that inhibit T_4 to T_3 conversion,[6] and it is likely that when such a drug is administered to a euthyroid individual, the thyrotrophs sense the lower intracellular T_3 concentration and respond by increasing their output of TSH. The increased TSH levels, in turn, stimulate the thyroid gland to synthesize and release additional thyroxine, which results in a rising serum T_4 concentration, often into the hyperthyroid range.[7,8] Euthyroidism is maintained in these individuals despite hyperthyroxinemia, however, because the conversion-inhibitory action of the drug on the liver[9] and kidneys[10] keeps blood levels of T_3 within the normal range, and most of the intracellular T_3 in nonpituitary cells comes from diffusion of circulating T_3 rather than from local generation.[5] These biochemical changes developed in the patient during propranolol therapy, and the greater TSH response to TRH (compared with her subsequent response when off therapy) suggests that this explanation of the sequence of events is very likely correct.

It is highly probable that the decline of the serum T_3 value well into the normal range and the elevation of the serum T_4 and resin uptake in the patient during propranolol therapy were the result of interference with T_4 monodeiodination by the drug, not a manifestation of hyperthyroidism, for these reasons: (1) in hyperthyroidism, there is no response of TSH to TRH administration, whereas in this patient there was a normal or slightly increased response, suggestive of latent hypothyroidism[11]; (2) in hyperthyroid patients with an autonomous nodule the thyroid scintigram shows suppression of the extranodular radioiodine uptake,[3] whereas in this patient there was no evidence of such suppression; and (3) when propranolol was discontinued, serum T_4 concentration rapidly returned to the normal, pretherapy range.

Euthyroid hyperthyroxinemia is a term that describes the clinical and biochemical findings of the syndrome seen in this patient.[2] A variety of causes has been described.[2] In euthyroid persons taking a conversion-inhibitory drug, such as propranolol, serum T_4 and FT_4I levels may increase, often into the hyperthyroid range, by the mechanism described above.[7,8] Total T_3 remains in the normal range,[7,8] however, and frequently declines.[10,12] The syndrome must be distinguished from true hyperthyroidism with anomalously normal T_3 concentration, so-called T_4

toxicosis, which occurs in some thyrotoxic patients who develop intercurrent illnesses or who ingest conversion-inhibitory drugs.[13] Distinction can be made by means of the TRH stimulation test: failure of TSH levels to rise after TRH injection is suggestive of hyperthyroidism in this setting, whereas a normal response (as in this patient) excludes it.[13]

The patient described in this report is unusual in that her progression from borderline T_3 toxicosis to hyperthyroxinemia was not the result of hyperthyroidism from her autonomous nodule, but rather was a drug-related phenomenon. Propranolol has been shown to revert elevated serum T_3 values to normal in hyperthyroid patients,[12,14] which occurred in this patient. Although the subsequent increase in serum T_4 concentration and FT_4I suggested the development of hyperthyroidism, TRH testing showed this not to be the case, and all values returned to normal when the drug was discontinued. Clearly in this patient the treatment of the disease mimicked the disease itself.

This patient was unusual in a number of respects. Although most patients who develop hyperthyroxinemia from propranolol are taking relatively high doses of the drug,[8,15] the patient was taking only 40 mg daily. In addition, the average increment in serum T_4 concentration following propranolol administration is only 18 nmol/L (1.4 μg/dL)[7] or less,[12,15,16] whereas in this patient T_4 rose by more than 39 nmol/L (3.0 μg/dL). However, because up to 14 percent of euthyroid patients given propranolol develop hyperthyroxinemia,[7] a drug-induced abnormality should be considered in any patient taking propranolol whose serum T_4 concentration is elevated.[8] Specifically, caution should be exercised in interpreting thyroid function tests in patients with suspected hyperthyroidism who are taking propranolol.

References

1. Hamburger JI: Evolution of toxicity in solitary nontoxic autonomously functioning thyroid nodules. J Clin Endocrinol Metab 1980; 50:1089–1093
2. Borst GC, Eil C, Burman KD: Euthyroid hyperthyroxinemia. Ann Intern Med 1983; 98:366–378
3. Charkes ND: Thyroid and whole-body imaging. In Ingbar SH, Braverman LE (eds): Werner's The Thyroid. A Fundamental and Clinical Text, ed 5. Philadelphia, JB Lippincott, 1986, pp 458–478
4. Chopra IJ: An assessment of daily production and significance of thyroidal secretion of 3,3′,5′-triiodothyroxine (reverse T_3) in man. J Clin Invest 1976; 58:32–40
5. Silva JE, Dick TE, Larsen PR: The contribution of local tissue thyroxine monodeiodination to the nuclear 3,5,3′-triiodothyronine in pituitary, liver and kidney of euthyroid rats. Endocrinology 1978; 103:1196–1207
6. Heyma P, Larkins RG, Campbell DG: Inhibition by propranolol of 3,5,3′-triiodothyronine formation from thyroxine in isolated rat renal tubules: An effect independent of beta adrenergic blockade. Endocrinology 1980; 106:1437–1441
7. Kristensen BO, Weeke J: Propranolol-induced increments in total and free serum-thyroxine in patients with essential hypertension. Clin Pharmacol Ther 1978; 22:864–867
8. Cooper DS, Daniels GH, Ladenson PW, Ridgway EC: Hyperthyroxinemia in patients with high-dose propranolol. Am J Med 1982; 73:867–871
9. van Noorden CJF, Wiersinga WM, Touber JL: Propranolol inhibits the in vitro conversion of thyroxine into triiodothyronine by isolated rat liver parenchymal cells. Horm Metab Res 1979; 11:366–370
10. Heyma P, Larkins RG, Higginbotham L, Ng KW: D-Propranolol and DL-propranolol both decrease conversion of L-thyroxine to L-triiodothyronine. Br Med J 1980; 281:24–25
11. Vagenakis AG, Rapoport B, Azizi F, et al: Hyperresponse to thyrotropin-releasing hormone accompanying small decreases in serum thyroid hormone concentrations. J Clin Invest 1974; 54: 911–918
12. Wiersinga WM, Touber JL: The influence of β-adrenoreceptor blocking agents on plasma thyroxine and triiodothyronine. J Clin Endocrinol Metab 1977; 45:293–298
13. Birkhauser M, Busset R, Burer T, Burger A: Diagnosis of hyperthyroidism when serum-thyroxine alone is raised. Lancet 1977; 2:53–56
14. Verhoeven RP, Visser TJ, Docter R, et al: Plasma thyroxine, 3,3″,5-triiodothyronine and 3,3′,5′-triiodothyronine during β-adrenergic blockade in hyperthyroidism. J Clin Endocrinol Metab 1977; 44: 1002–1005
15. Reeves RA, From GLA, Paul W, Leenen FHH: Nadolol, propranolol, and thyroid hormones: Evidence for a membrane-stabilizing action of propranolol. Clin Pharmacol Ther 1985; 37:157–161
16. Williams ES, Jacobs HS: Effect of propranolol on serum-thyroxine. Lancet 1970; 2:829–830