MEDICAL TREATMENT OF TOXIC GOITER IN AN AREA OF IODINE DEFICIENCY*

FEREYDOON AZIZI, M.D.

From the Department of Medicine, Taleghani Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Islamic Republic of Iran.

ABSTRACT

The response to methimazole [1-methyl-2-mercapto-imidazole (MMI)] therapy, 10 mg twice daily in 15 patients and propylthiouracil (PTU) therapy, 100mg twice daily in 10 patients with diffuse toxic goiter was evaluated in an area of iodine deficiency (Tehran).

The mean free T_4 index (FT₄I) decreased from 22.7± 6.8 (± SD) to 10.8 ± 2.8 In MMI-treated, and from 25.1±6.8 to 13.2 ± 2.1 in PTU-treated patients, two weeks after treatment. The FT₄I further decreased to 6.8 ± 4.3 and 8.5 ± 2.1 after four weeks of MMI and PTU administration, respectively. The mean free T_3 index (FT₃I) was 415 ± 90 , 162 ± 44 and 117 ± 46 in MMI treated and 430 ± 80 , 210 ± 45 and 140 ± 53 in PTU treated patients before and two and four weeks after treatment, respectively. The mean FT₄I and FT₃I had decreased more in the MMI treated groups as compared to the PTU treated patients, two weeks after treatment. In patients treated with MMI or PTU, 11 of 25 (44%) had subnormal FT₄I after four weeks of treatment, of whom one had increased serum TSH.

These results indicate that treatment with less than the recommended doses of thionamide compounds causes a rapid decline of thyroid hormone indices in patients residing in Tehran. The dosage of thionamide compounds as well as the duration of therapy with the initial doses necessary to induce euthyroidism, should be evaluated in various parts of the world.

MJIRI, Vol.2, No.2, 119-122, 1988

INTRODUCTION

In hyperthyroid patients treated with thionamide compounds, a reduction of the serum concentrations of thyroid hormones occurs after a latent period. Thus, it has been shown that thionomide compounds do not effect the release of thyroid hormones. The latent period is influenced by the quantity of hormones initially present in the gland, their rate of release, and the dosage of thionamide used. 1-3

We have previously reported that treatment with the recommended doses of methimazole (MMI) rapidly causes hypothyroidism in patients residing in Tehran, an area of iodine deficiency.4

In the present study, we have evaluated the effect of lower doses of MMI and propylthiouracil (PTU) in patients with diffuse toxic goiter and in pregnant patients with hyperthyroidism in Tehran.

MATERIALS AND METHODS

Untreated patients with diffuse toxic goiter received antithyroid drugs for four weeks. A group of 15 patients, 10 women and five men, received MMI, 10 mg twice daily (group A). Another group of 10 patients,

^{*} A portion of this work was presented at the Third Asian & Oceana Thyroid Association Meeting, Bangkok, 1986.

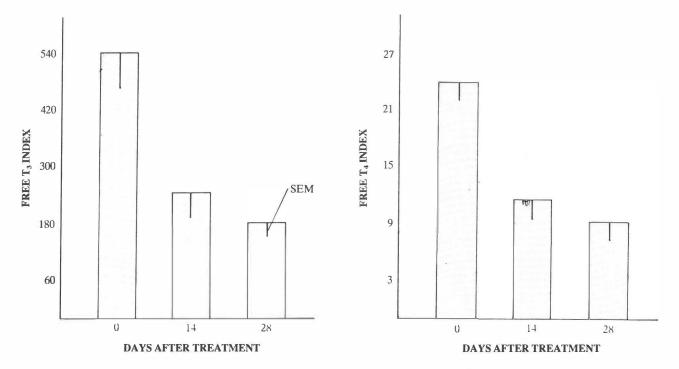


Fig 1. The effect of PTU therapy (100 mg twice daily) on mean $F\Gamma_4I$ and $F\Gamma_3I$ in 10 patients with diffuse toxic goiter residing in Tehran. Normal ranges: $F\Gamma_4I$, 4.5-13.0; $F\Gamma_3I$, 50-200.

seven women and three men, received PTU, 100 mg twice daily (group B). Methimazole, 10 mg twice daily, was also given to eight pregnant patients with diffuse toxic goiter for four weeks (group C).

Clinical status; serum concentrations of T_4 , T_3 and TSH as well as T_3 resin uptake were evaluated before and after treatment. The free T_4 index (FT₄I) and free T_3 index (FT₃I) then were calculated.⁵

Normal ranges in 180 normal subjects were: FT_4I , 4.5-13.5; and FT_3I , 80-200.

RESULTS

Group A: In patients treated with MMI, 10 mg twice daily, serum FT₄I decreased from 22.7 ± 6.8 to 12.1 ± 2.5 (p < 0.001) eight days after treatment, and 10 of 15 patients achieved normal FT₄I values. 14 days after treatment, FT₄I had decreased further to 10.8 ± 2.8 . 13 of 15 patients had a normal FT₄I at this time. Four weeks after treatment, the mean FT₄I was 6.8 ± 4.3 . It was subnormal in seven (46%) patients, one of whom had increased serum TSH. Minor symptoms of weight gain, dry skin and weakness were reported by four patients. FT₃I values were 415 ±60 , 197 ±36 , 162 ± 44 and 117 ± 46 , before treatment; and 8, 14, and 28 days after treatment, respectively. The age of the patients, size of goiter, and baseline values of the FT₄I

and FT₃I were not significantly different in those who became hypothyroid and those who did not.

Group B (Fig. 1): In patients treated with PTU, 100 mg twice daily. FT_4I decreased from 25.1 ± 6.8 to 13.2 ± 2.1 (p < 0.001) two weeks after treatment.

In seven of 10 patients, FT_4I had decreased tonormal values at this time. Four weeks after treatment, mean FT_4I was 8.5 ± 2.1 and it was subnormal in four (40%) patients. FT_3I values were $430\pm80.210\pm45$, 140 ± 35 , before, and 14 and 28 days after treatment, respectively. At the end of four weeks, one patient had a subnormal FT_3I . None had an increase in TSH.

The effects of MMI and PTU on thyroid hormone indices are compared in Table I. It appears that, at least two weeks after treatment, the effect of MMI on inhibition of thyroid hormone synthesis is slightly greater than PTU.

Group C: The effect of MMI therapy (10 mg twice daily for four weeks) on mean FT₄I and FT₃I levels in eight patients with diffuse toxic goiter is shown in Table II.

After four weeks of treatment, FT_4I was subnormal in three (40%) patients. Thereafter, all patients were effectively maintained euthyroid with a daily dose of 5 mg MMI throughout pregnancy. In one patient, the dosage had to be diminished to 2.5 mg daily.

F. Azzizi, M.D.

Table I: The effect of treatment with thionamide derivatives on mean FT₄I in patients with diffuse toxic goiter.

RX	FT ₄ I			FT ₃ I		
	MMI*	PTU**	P	MMI	PTU	P
Before 2 weeks 4 weeks	22.7± 6.8 10.8± 2.8 6.8± 4.3	13.2±2.1 8.5±2.1	NS < 0.05 NS	415± 90 162± 44 117± 46	430± 80 210± 45 140± 35	NS <0.02 NS

^{*} Methimazole 10 mg twice daily: 15 patients

DISCUSSION

In a previous study we have shown that treatment of patients with toxic goiter with daily doses of 30 mg MMI, which causes mild to moderate decrease in thyroid hormone concentration in areas of iodine sufficiency, 2.6 results in clinical and biochemical evidences of hypothyroidism in almost half of patients treated for four weeks in Tehran. The present study demonstrates that treatment of diffuse toxic goiter with divided doses of 10 mg MMI or 100 mg PTU twice daily in patients residing in Tehran, reduces free thyroid hormone indices to half of pre-treatment values within two weeks. 11 of 25 (44%) patients had FT₄I values below the normal range after one month of therapy while at that time, one patient had clinical evidence of hypothyroidism and elevated serum TSH concentration.

A rapid fall in FT₄I and FT₃I was also observed in pregnant thyrotoxic patients after administration of 10 mg MMI twice daily. In contrast to high doses of MMI needed to treat thyrotoxicosis in pregnant women in areas of iodine sufficiency, ⁷ it appears that low doses are effective in areas of iodine deficiency, perhaps minimizing the chance of adverse reactions in mother and fetus.

Thionamide compounds inhibit iodination of thyroglobulin tyrosine residues and the coupling of iodotyrosines, most likely by inhibiting thyroid peroxidase. $^{2.8}$ Therefore thionamide drugs inhibit the synthesis of thyroid hormones; however, they do not affect the rate of release of thyroid hormones. Propylthiouracil (PTU) also impairs the conversion of T_4 to T_3 in the peripheral tissues, but MMI does not. 9

Thionamides were introduced intoclinical medicine in 1943, ¹⁰ a time when in the U.S. iodide deficiency had already been prevented by provision of iodized salt. Therefore, the initial studies of the effect of thionamide compounds in the treatment of hyperthyroidism were carried out in areas of iodine sufficiency. In 1950, doses of PTU recommended by Astwood¹¹ and Williams¹² were 200-400 mg daily (average, 300 mg) and were

increased to 300-600 mg daily in later reports. ¹³ The recommended dosage of MMI is about one tenth that of PTU. It has been suggested that treatment with the usual recommended dosage and regimen restores normal metablic rate and serum concentration of thyroid hormone within 6 weeks ¹³ to 3 months. ¹⁴

Environmental iodine intake may affect the response to thionamide therapy in patients with hyperthyroidism in several ways. Firstly, thyroid hormone stores within the thyroid follicles may be very little in patients residing in an area of iodine deficiency. Therefore inhibition of synthesis of thyroid hormones by MMI may cause a rapid decline in serum thyroid hormone concentration in patients residing in areas of iodine deficiency. Iodine deficiency has been clearly demonstrated in Tehran and suburbs. 15 Secondly, intrathyroidal metabolism of MMI may be decreased in patients residing in areas of iodine deficiency. Reduced intrathyroidal metabolism of thionamide compounds previously was found in the thyroids of rats fed a low iodine diet, despite a great increase in the size and peroxidase activity of the thyroid. 16.17 Thirdly, MMI inhibition of thyroid peroxidase is competitive with iodide¹⁸ and high concentrations of intrathyroidal

Table II: FT₄ and FT₃ indices in eight pregnant patients with diffuse toxic goiter before and after treatment with methimazole (20 mg/d for four weeks).

	FI	Γ_4 I	FT ₃ I		
Treatment	(Before)	(After)	(Before)	(After)	
NO. 1	13.2	9.2	410	100	
2	24.0	1.4	530	90	
3	19.6	2.2	490	95	
4	26.0	8.0	680	230	
5	20.5	12.2	720	165	
6	19.0	7.2	450	190	
7	18.5	9.2	520	140	
8	27.2	0.5	350	82	
Mean	26.6	6.2	518	136	
SD	4.9	4.3	127	54	
Normal range	4.5-13.0		80-200		

^{**} Propylthiouracil 100 mg twice daily; 10 patients

Medical treatment Toxic Goiter

iodide may effect the inhibitory action of low levels of MMI.8

We conclude that recommended dosages and regimens of thionamide administration cannot be employed for the treatment of diffuse toxic goiter in Tehran and perhaps in other areas of iodine deficiency. In such patients we recommend starting doses of 10 mg MMI or 100 mg PTU, twice daily, for two weeks, and 5 mg twice daily, for an additional two weeks. Evaluation of serum concentrations of thyroid hormones after two and four weeks of therapy may be helpful in deciding further optimum dosage of MMI or PTU. Similar studies should be carried out in other parts of the world, in particular in countries with inadequate daily iodide intake.

REFERENCE

- 1- Langer R, Greer MA: Antithyroid substances and naturally occurring goitrogens. Basel: Karger, 178, 1977.
- 2- Richards JB, Ingbar SH: The effects of propylthiouracil and perchlorate on the biogenesis of thyroid hormone. Endocrinology, 65 (2): 198-207, 1959.
- 3- Solomon DH: Treatment: antithyroid drugs, surgery, radioiodine; selection of therapy. In: Werner SC, Ingbar SH, (eds). The Thyroid. Hagerstown: Harper and Row, 814, 1978.
- 4- Azizi F. Environmental iodine intake affects the response to methimazole in patients with diffuse toxic goiter. J Clin Endocrinol Metab, 61 (2); 374-7, 1985.
- 5- Sawin CT, Chopra. D, Albano J, Azizi F, The free triiodothyronine (T3) index. Ann Intern Med 88 (4): 47-7, 1978.
- 6- Greer MA, Kammer H, Bouma DJ: Short-term antithyroid drug

- therapy for the thyrotoxicosis of Graves's disease. N Engl J Med 297 (4): 173-6, 1977.
- 7-Burrow GN: The management of thyrotoxicosis in pregnancy. N Engl J Med 313 (9): 562-5, 1985.
- 8-Taurog A: Thyroid peroxidase and thyroxine biosynthesis. Recent Prog Horm Res 26:189, 1970.
- 9- Geffner DL. Azukizawa M, Hershman JM: Propylthiouracil blocks extrathyroidal conversion of thyroxine to triiodothyronine and augments thyrotropin secretion in man. J Clin Invest 55 (2): 224-9, 1975.
- 10- Astwood EB: Treatment of hyperthyroidism with thiourea and thiouracil. JAMA 122: 78-81, 1943.
- 11- Astwood EB: Clinical use of antithyroid drugs. In: Soskin S, ed. Progress in Clinical Endocrinology. New York: Grune and Stratton, 79, 1950.
- 12- Williams RH: Thyroid. In: Williams RH, ed. Textbook of Endocrinology. Philadelphia: Saunders, 131, 1950.
- 13-Ingbar SH, Woeber KA: The thyroid gland. In: Williams RH, ed. Textbook of Endocrinology, Philadelphia: Saunders, 117-247, 1981.
- 14- McClung MR, Greer MA: Treatment of hyperthyroidism. Annu Rev Med 31: 385-404, 1980.
- 15- Azizi, F, Kimiagar M, Navai L, Nafarabadi M, Mostafavi H: Goiter in Tehran and Suburbs. Recent Progress in thyroidology. Proceedings of the 3rd Asia & Oceania Thyroid Association. Dec.
- 16- Machant B, Papapetrou, PD, Alexander WB: Relation between thyroid iodine content and the accumulation and oxidation of [35-s] methimazole in the rat. Endocrinology 97 (1): 154-61, 1977.
- 17- Nakashima T, Taurog A, Riesco §: Mechanism of action of thioureylene antithyroid drugs: factors effecting intrathyroidal metabolism of propylthiouracil and methimazole in rats. Endocrinology 103 (6): 2187-97, 1978.
- 18- Degroot LJ, Davis AM: Studies on the biosynthesis of iodotyrosines: a soluble thyroidal iodide-peroxidase tyrosine-iodinase system. Endocrinology 70: 492-504, 1962.