Long Term Antithyroid Drug Therapy for Intractable Cases of Graves' Disease

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Synopsis

Among the 504 patients with Graves' disease in whom the author initiated antithyroid drug therapy between 1956 and 1968 are 14 to whom the administration of antithyroid drug has been continued for 8 to 21 years because of recurrence shortly after the discontinuation of drugs. During these periods, no side effects were observed and three patients went into complete remission after 8, 9 and 20 years of antithyroid drug administration, respectively.

It is suggested therefore that the long term administration of antithyroid drugs can be a useful treatment for intractable cases.

When symptoms or signs of hyperthyroidism recur after a year of treatment with antithyroid drugs, it has been recommended that such patients be treated by either subtotal thyroidectomy or radioactive iodine. We have observed 14 patients with Graves' disease treated with antithyroid drugs for 8 to 21 years because of repeated recurrences of symptoms shortly after the discontinuation of medication and of their reluctance to be treated by ablative methods.

The benign course of these patients strongly suggests that chronic antithyroid drug therapy may be useful in selected patients with Graves' disease who do not remain euthyroid after stopping drug therapy.

Subjects and Methods

The present study concerned 14 patients among 504 patients in whom antithyroid drug therapy for more than six months was initiated by the author between 1956 and 1968. Among the 504 cases, 140

went into remission for more than two years after stopping medication, 5 became hypothyroid between 5 and 20 years after stopping medication, 35 received operations because of recurrence, 140 received radioactive iodine treatments because of recurrence, 170 escaped the author's observation within two years after stopping therapy and 14 were treated with antithyroid drug for 8 to 21 years. These 14 cases have been followed by the author throughout the study. Propylthiouracil (PTU) was used in five cases and methimazole (MMI) was used in the other nine. Results for each patient are shown in Table 1. Maintenance doses ranged from 25 to 150 mg with PTU and 2.5 to 15 mg with MMI. Some patients took their medication b.i.d. or t.i.d. while others took the drugs once a day.

They were followed at 1- to 3-month intervals and were maintained euthyroid by adjusting the dose. In all patients, drugs were discontinued for 2 to 4 weeks every 6 to 12 months. However, in these patients, antithyroid drug therapy had to be reinstituted because of a recurrence of the symptoms or signs of hyperthyroidism and elevated values of PBI or serum T_4 .

The thyroid suppression test was performed every one or two years in all patients and was carried out as follows. The antithyroid drug was discontinued and the following day T_3 (25 μ g t.i.d.) was begun and continued for 7 days. On the seventh day, 5 to 10 μ Ci of 131 I was administered orally and 24 hours later thyroid 131 I uptake was determined.

The thyroid suppression test was considered abnormal when the uptake was greater than 40% and normal when it was less than 20%. Values between 20 and 40% were not observed in any of the 14 patients.

In our laboratory, normal values for serum T_4 and T_3 concentrations ranged between 5 and 12 $\mu\text{g/dl}$ and 80 to 200 ng/dl , respectively. Complete blood counts, urinalysis and blood chemistries were performed in all patients at frequent intervals.

Results

The most recent results of thyroid function tests in these 14 patients are summarized in Table 1. Serum T_4 and T_3 concentrations were normal in all subjects. However, the thyroid suppression test was still abnormal in 11 patients who are still receiving PTU or MMI, and was normal in 3 patients (No. 2, 11 and 14) who were not receiving the drugs. In patient #2, the thyroid suppression test became normal after 20 years of PTU therapy and he has remained euthyroid for one and a half years off therapy. In patients #11 and #14, the

thyroid suppression test became normal after nine and eight years of MMI therapy respectively and they have remained euthyroid for one and 4 years after discontinuing MMI, respectively. Based on the clinical course and laboratory studies, no side effects of the drug were observed in any of the patients.

Discussion

The course of Graves' disease seems to be variable. According to several reports on a large number of patients, about 35 to 55% of them remain in permanent remission after stopping antithyroid drugs. (Hershman *et al.*, 1966; Shizume *et al.*, 1970; Ito *et al.*, 1974; Thalassions *et al.*, 1974) Greer *et al.*, (1977) recently reported that the lasting remission rate after 3 or 4 months of treatment with antithyroid drugs was as good as that after the treatment for one year or more. McLarty *et al.* (1973) reported that 4 of 28 patients became eu-

Table 1. Results of thyroid function tests in 14 patients treated with antithyroid drug for 8 to 21 years

Patient	Sex	Age at the Initiation of Therapy	Drug	Duration of Therapy (year)	Maintenance Dose (mg/d)	Most Recent Values			Side Effects	Comments
						T_4 ($\mu\text{g/dl}$)	T_3 (ng/dl)	^{131}I uptake after T_3 (%)*		
1	F	39	PTU	21	100	8.9	194	41	none	
2	M	53	PTU	20	50	6.8	182	9	none	discontin. 1.5 years ago
3	F	31	MMI	15	15	10.2	190	60	none	
4	F	16	MMI	13	10	7.8	162	41	none	
5	F	36	MMI	11	5	9.1	190	45	none	
6	F	49	MMI	11	2.5	8.2	142	42	none	
7	F	36	PTU	11	25	8.8	108	43	none	
8	F	34	MMI	10	10	5.4	135	50	none	
9	M	36	MMI	9	5	10.1	170	46	none	
10	M	39	PTU	9	50	7.1	154	44	none	
11	F	30	MMI	9	2.5	10.3	153	15	none	discontin. 1 year ago
12	F	25	MMI	8	5	7.2	105	57	none	
13	M	25	PTU	8	150	9.3	117	62	none	
14	F	42	MMI	8	5	8.5	169	18	none	discontin. 4 years ago

PTU: propylthiouracil MMI: methimazole

* 24 hr thyroidal ^{131}I uptake after administration of T_3 (25 μg : t.i.d.) for 7 days.

thyroid after treatment with propranolol which had no direct effect on thyroid function. Wood *et al.* (1972) reported that among 15 patients whose only therapy was a course of thionamides completed 20 to 27 years earlier, one patient was frankly hypothyroid, and 5 patients showed subnormal response to TSH which suggested the presence of subclinical hypothyroidism. In my study, 140 of 334 patients became euthyroid at least for two years after stopping antithyroid drugs and 5 patients became hypothyroid 5 to 20 years after stopping antithyroid drug. These results suggest that quite a number of patients with Graves' disease might develop spontaneous remissions after their active stages were treated with antithyroid drugs and some of them become hypothyroid as part of the natural course of the disease itself. On the other hand, my study shows that in some patients the basic process of the disease continues for 8 to 20 years and then becomes euthyroid and in other patients it continues for more than 10 to 20 years. If the antithyroid therapy is halted in the latter cases they become hyperthyroid soon. The incidence of such patients may not be infrequent because most of the candidates who might have followed such a course may have been treated either by radioactive iodine or surgery. Before the modern treatment became available they probably died of cardiac failure because of a long-continued hyperthyroid state. Objections to the long-term treatment with antithyroid drugs for such patients are the occurrence of drug toxicity and poor patient compliance. However, antithyroid drug therapy has the advantage of not resulting in permanent hypothyroidism, although hypothyroidism occasionally occurs years after therapy. Side effects of antithyroid drugs usually appear within one or two months after the institution of treatment, and rarely occur years later (Shizume *et al.*, 1970). No side effects during 8 to 21 years of therapy were observed in

the present study. As far as patient compliance is concerned, little difficulty was observed in these patients after the first year of therapy. Based on the present experience and in view of the high incidence of hypothyroidism after radioiodine therapy (Dunn and Chapman, 1964), the long-term administration of antithyroid drugs should be considered as an alternative choice for the treatment of intractable Graves' disease.

Acknowledgements

The author wishes to express his thanks to Drs. Minoru Irie, Shigenobu Nagataki, Fukashi Matsuzaki, Yoshimasa Shishiba, Hiroyuki Suematsu, Toshiro Tsushima and Kazue Takano for their cooperation during my observation of these patients reported in this paper.

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