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Sodium Ipodate and Methimazole in the Long-Term Treatment of Hyperthyroid Graves' Disease

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A prospective study was conducted to evaluate the effect of prolonged treatment of hyperthyroid Graves' disease with methimazole (MMI) for 12 months or Na ipodate for only 6.6 ± 1.1 months, since the drug had to be discontinued because of persistent or recurrent hyperthyroidism during treatment. The eight patients who were treated with MMI alone for 12 months became euthyroid, and seven remained in remission for at least 6 months after MMI was discontinued. In contrast, only two of 10 patients treated with Na ipodate alone became euthyroid and remained so during therapy. Na ipodate was discontinued in the eight patients who did not respond, and they were then treated with MMI. One patient had recurrent hyperthyroidism after NA ipodate was discontinued, and she was then treated with MMI. MMI was efficacious in treating these nine patients, and all patients were euthyroid by the third month of MMI administration. Five of these nine patients remained euthyroid for at least 6 months after MMI was discontinued, a remission rate that was not significantly differrent from that observed in the eight patients treated only and initially with MMI (Fisher's Exact Test). There was no significant change in serum thyroid peroxidase antibodies during treatment with MMI alone, Na ipodate alone, or Na ipodate followed by MMI. In conclusion, the present study strongly suggests that Na ipodate is not useful in the long-term treatment of Graves' hyperthyroidism since only two patients could be successfully treated for 12 months, one of whom had a recurrence 6 months later, and that MMI is less efficacious in reducing serum thyroid hormone concentrations following Na ipodate withdrawal due to the iodide load associated with Na ipodate administration.

THE ADMINISTRATION of iodine-rich cholecystogrpahic x-ray contrast agents to hyperthyroid patients induces a marked and rapid decrease in serum 3,3',5-triiodothyronine (T_3) concentrations, a slight decrease in serum thyroxine (T_4) concentrations, and a striking increase in serum 3,3',5'-triiodothyronine (reverse T_3 [rT_3]) concentrations.[1-3] These serum thyroid hormone changes are primarily due to the inhibitory effect of oral cholecystographic x-ray contrast agents on outer-ring 5'deiodination of T_4 to the more active iodothyronine, T_3.[3,4-8] However, since contrast agents release iodide during their peripheral metabolism, the increase in serum iodide contributes to the diminution of serum thyroid hormone concentrations by blocking hormone release from the thyroid.

Short-term treatment of hyperthyroid patients with oral cholecystographic agents either alone or with antithyroid drugs has been shown to be more effective in reducing serum T_3 concentration than antithyroid drug treatment alone or with stable iodine.[3,9-11] Furthermore, the decrease in serum thyroid hormone concentrations following therapy with these agents was associated with a more rapid amelioration of clinical symptoms.[3,11] In contrast, the long-term treatment of hyperthyroid patients with oral cholecystographic agents has resulted in variable responses, with escape from the drug being observed in some patients.[12-19]

In the present study, we have compared the effects of long-term treatment with methimazole (MMI) or Na ipodate on serum thyroid hormone concentrations in patients with hyperthyroid Graves' disease. Furthermore, the effect

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Table 1. Serum T4 and T3 Concentrations in Patients Treated With MMI, Na Ipodate, and Na Ipodate and Then With MMI

	Months of Treatment											
	0	1	2	3	4	5	6	7	8	9	10	11	12
MMI													
T_4 (nmol/L)	265 ± 30 (8)	96 ± 18 (8)	102 ± 22 (8)	117 ± 13 (8)	120 ± 11 (8)	114 ± 12 (8)	138 ± 16 (8)	107 ± 4 (8)	119 ± 13 (8)	122 ± 15 (8)	107 ± 7 (8)	132 ± 15 (8)	133 ± 16 (8)
T_3 (nmol/L)	5.9 ± 0.9 (8)	2.0 ± 0.3 (8)	1.9 ± 0.4 (8)	2.0 ± 0.3 (8)	2.0 ± 0.2 (8)	1.7 ± 0.2 (8)	2.2 ± 0.3 (8)	1.5 ± 0.1 (8)	1.7 ± 0.1 (8)	1.7 ± 0.1 (8)	1.6 ± 0.1 (8)	1.8 ± 0.1 (8)	1.9 ± 0.2 (8)
Na Ipodate													
T_4 (nmol/L)	231 ± 12 (10)	190 ± 15 (10)	218 ± 20 (10)	201 ± 23 (10)	198 ± 29 (8)	173 ± 20 (5)	175 ± 20 (5)	169 ± 22 (5)	161 ± 15 (4)	158 ± 8 (3)	154 ± 1 (2)	157 ± 13 (2)	180 ± 22 (2)
T_3 (nmol/L)	4.6 ± 0.5 (10)	2.3 ± 0.4 (10)	2.5 ± 0.4 (10)	2.2 ± 0.3 (10)	2.0 ± 0.4 (8)	1.8 ± 0.3 (5)	1.6 ± 0.3 (5)	1.6 ± 0.3 (5)	1.6 ± 0.3 (4)	1.6 ± 0.3 (3)	1.1 ± 0.0 (2)	1.2 ± 0.1 (2)	1.2 ± 0.2 (2)
Na Ipodate discontinued and MMI administered (months indicate time during MMI administration)													
T_4 (nmol/L)	221 ± 19 (9)	154 ± 6 (9)	125 ± 12 (9)	100 ± 14 (9)	104 ± 15 (9)	118 ± 12 (9)	127 ± 14 (9)	99 ± 14 (9)	102 ± 5 (9)				
T_3 (nmol/L)	2.3 ± 0.2 (9)	2.7 ± 0.2 (9)	2.3 ± 0.2 (9)	1.9 ± 0.2 (9)	1.9 ± 0.1 (9)	2.0 ± 0.1 (9)	2.0 ± 0.2 (9)	1.7 ± 0.3 (9)	1.7 ± 0.2 (9)				

NOTE. Results are means ± SE; the number in parentheses indicates the number of patients evaluated at each time. Normal ranges: T_4, 64.3-141.5 nmol/L; T_3, 1.0-2.5 nmol/L.

of MMI in restoring euthyroidism in patients unsuccessfully treated with Na ipodate is reported.

SUBJECTS AND METHODS

Eighteen patients with hyperthyroid Graves' disease participated in the study after informed consent was obtained. All patients resided in the Parma area, where the mean thyroid iodine excretion is 80 μg I/g creatinine. Diagnosis of active Graves' disease was confirmed by clinical examination and by increased serum T_4 and T_3 concentrations with suppressed serum thyrotropin (TSH) values and elevated radioactive thyroid iodine uptakes (RAIU) measured 6 and 24 hours following the administration of 5 μCi ^{131}I. Eight women 39 ± 4.4 years of age were treated with 20 mg MMI daily, and 10 patients, nine women and one man 39.9 ± 3.1 years of age, were treated with 1 g Na ipodate daily.

In eight patients, MMI administration was maintained at 20 mg daily for the first 3 months, and the dose of MMI was then adjusted according to clinical and laboratory responses. In 10 patients treated with Na ipodate, the drug was withdrawn when the patients did not maintain evidence of clinical improvement and/or serum T_3 concentrations increased after the initial decrease (six patients), and/or when serum T_4 concentrations were 5 μg/dL over baseline values (two patients), suggesting the presence of hyperthyroidism. However, all 10 patients were treated with Na ipodate for at least 3 months; two patients were treated for 12 months, one patient for 9, one for 8, one for 7, three for 4, and two for 3 months. Following withdrawal of Na ipodate, the patients were treated with 20 mg MMI daily for 3 months and, as in the patients treated with MMI only, the dose of MMI was then adjusted according to the clinical and laboratory responses. These patients were considered as a group (Na ipodate-MMI group in Table 1). Their serum thyroid hormone concentrations at the time of Na ipodate withdrawal represent the new baseline values for this group.

All patients were clinically evaluated at monthly intervals including body weight and heart rate measurements, and thyroid function tests were obtained monthly for 12 months and every other month thereafter for 6 months. Thyroid RAIU was again measured in all patients 12 months after the onset of the study.

Serum samples were kept frozen at −20°C until analysis. Serum T_4 and T_3 concentrations were assayed by radioimmunoassay (RIA) with materials obtained from Ares-Serono (Milan, Italy). Serum TSH concentrations were measured by a sensitive RIA (TSH-S) with materials obtained from Ares-Serono. Serum antithyroid peroxidase antibodies (AbTPO) were assayed by RIA using materials obtained from Henning (Berlin, Germany).

To compare changes in serum thyroid hormone concentrations during MMI treatment in patients previously treated with Na ipodate with values in patients treated with MMI alone, individual absolute values have been transformed to the percent of the respective values measured at the time MMI treatment was begun. All values are reported as the mean ± SE. Student's *t* test was used to compare mean values of the two groups of subjects; one-way ANOVA and Duncan's tests to evaluate hormone changes during treatment in each group of patients; two-way ANOVA to compare hormone values between different groups of patients; and Fisher's Exact Test to evaluate the prevalence of different results between two groups. Statistical evaluations have been conducted with the aid of an IBM personal computer using the NWA Statpak program (NorthWest Analytical, Portland, OR).

RESULTS

Thyroid RAIU

In patients treated with MMI alone, thyroid RAIU values at 6 and 24 hours were 74% ± 5% and 70% ± 31%,

respectively, before MMI was begun. Twelve months later, 17 ± 6 days after MMI was discontinued, thyroid RAIU values decreased significantly ($P < .001$, Student's t test) with values at 6 and 24 hours of 33.5% ± 2% and 44% ± 2%, respectively.

In patients treated with Na ipodate, thyroid RAIU values at 6 and 24 hours were 59% ± 7% and 63% ± 5%, respectively, before treatment was begun. These values were not different (Student's t test) from those obtained in the MMI-treated patients. Twelve months later (12 ± 3 days after all therapy was discontinued), thyroid RAIU was measured in patients who had continued Na ipodate treatment (two patients) and in those who had discontinued Na ipodate and begun MMI treatment (eight patients). In the eight patients who began MMI treatment after Na ipodate was withdrawn (6 ± 0.8 months before RAIU was obtained), thyroid RAIU values at 6 and 24 hours, 40% ± 6% and 47% ± 6%, respectively, were significantly lower ($P < .05$, Student's t test) than those observed in the same patients before treatment, but were not significantly different (Student's t test) from those obtained at 12 months (17 ± 6 days after MMI was discontinued) in the eight women treated with MMI alone.

Serum T_4 Concentrations (Table 1)

In patients treated with MMI alone, basal serum T_4 concentrations were 265 ± 30 nmol/L, and they markedly decreased during treatment ($P < .001$, one-way ANOVA). One month after MMI treatment was begun, the mean serum T_4 concentration was normal and all individual values, except for one were within the normal range. During the first 3 months of treatment, serum T_4 concentrations in patients treated with MMI were significantly lower than those observed in patients treated with Na ipodate ($P < .01$, two-way ANOVA).

In patients treated with Na ipodate, basal serum T_4 concentrations were 231 ± 12 nmol/L, a value not different from that of the MMI-treated patients (Student's t test). Serum T_4 concentrations at months 1, 2, and 3 of treatment were 190 ± 15, 218 ± 20, and 201 ± 23 nmol/L, respectively, not significantly different from baseline (one-way ANOVA, Duncan's tests). Na ipodate was discontinued in eight patients because of recurrent symptoms and/or laboratory evidence of escape at various times after the third month of therapy, and MMI treatment was begun. Two of these patients had serum T_4 values greater than 5 μg/dL above baseline. Only two patients were treated with Na ipodate alone for the full 12 months; one remained euthyroid and one had recurrent hyperthyroidism 6 months later, requiring MMI therapy.

In the nine patients treated with Na ipodate and then with MMI, serum T_4 concentrations before starting MMI were increased to 221 ± 19 nmol/L. Serum T_4 concentrations significantly decreased ($P < .001$, one-way ANOVA) over the next 8 months, reaching a nadir of 100 ± 14 nmol/L 3 months after MMI was begun. During MMI therapy, all except two individual T_4 values were in the normal range.

The percent decrease in serum T_4 concentrations compared with their respective values before MMI treatment was begun was significantly greater ($P < .02$, two-way ANOVA) in patients treated from the beginning with MMI than in those patients treated with MMI after Na ipodate was discontinued (Fig 1).

Serum T_3 Concentrations (Table 1)

In patients treated with MMI alone, basal serum T_3 concentrations were 5.9 ± 0.9 nmol/L, and they markedly decreased during treatment ($P < .01$,one-way ANOVA). In 1 month, the mean serum T_3 concentration was in the normal range (2.0 ± 0.3 nmol/L, $P < .001$ v basal values, Duncan's test) and was normal in six of the eight patients. By the third month, serum T_3 concentrations were 2.0 ± 0.3 nmol/L, and all individual values except for one were in the normal range.

In patients treated with Na ipodate, basal serum T_3 concentrations were 4.6 ± 0.5 nmol/L, similar to basal values in MMI-treated patients. During Na ipodate administration, serum T_3 concentrations decreased significantly by 1 month of treatment to 2.3 ± 0.4 nmol/L ($P < 0.001$ v basal value, Duncan's test). At the end of the third month of Na ipodate administration, serum T_3 concentrations were 2.2 ± 0.3 nmol/L; eight of the 10 individual values were in the normal range. No significant difference in serum T_3 concentration (two-way ANOVA) was observed during the first 3 months of treatment between patients treated with MMI alone and Na ipodate alone. In patients who continued on Na ipodate therapy after the third month of treatment (number of patients reported in Table 1), serum T_3 concentrations remained in the normal range. Na ipodate was discontinued at various times after the third month because of an increase in the serum T_3 concentration in six patients of 28.2 ± 9 ng/dL above the lowest values observed during Na ipodate therapy ($P < .02$, paired Student's t test). During the first 3 months of MMI

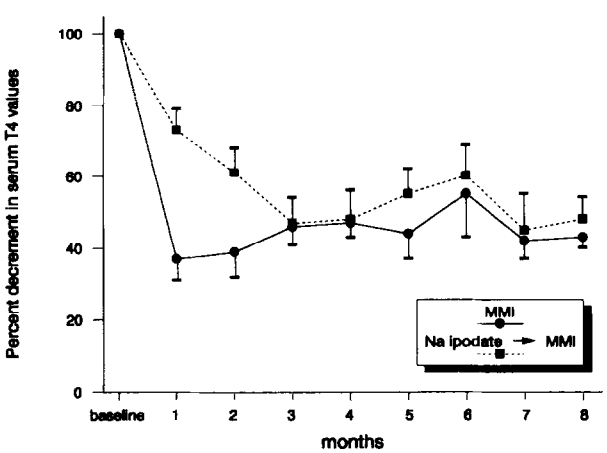

Fig 1. Percent decrease in serum T_4 concentrations in patients treated with MMI alone and in those treated with Na ipodate and then with MMI. The months on treatment represents the time patients received MMI, whether from the beginning or after Na ipodate was withdrawn. The percent decrease was significantly greater ($P < .02$, two-way ANOVA) in patients treated with MMI only than in those treated with Na ipodate and then with MMI; bars represent SE.

treatment following Na ipodate withdrawal, the serum T_3 concentration did not significantly decrease, but it did decrease ($P < .01$, one-way ANOVA) during the following 3 months. After 6 months of MMI treatment, all individual serum T_3 values were in the normal range.

There was a significant decrease in serum T_3 concentrations compared with basal values in patients treated with MMI alone, but not in patients treated with MMI after Na ipodate was discontinued (Fig 2).

Serum TSH Concentrations

Serum TSH concentrations were undetectable in all subjects in both groups before treatment was begun. In patients treated with MMI alone, five had detectable serum TSH values after 3 months of treatment (TSH-S values ranged between 0.5 and 3.8 mU/L; $P < .01$ *v* Na ipodate group, Fisher's Exact Test), and all subjects had detectable TSH values at the end of 12 months (TSH-S values ranged between 0.5 and 2.2 mU/L).

Nine of 10 patients treated with Na ipodate had undetectable serum TSH values during Na ipodate administration ($P < .01$ *v* MMI group, Fisher's Exact Test). The one patient whose serum TSH level increased into the normal range (0.58 mU/mL) was euthyroid 6 months after Na ipodate was discontinued.

The patients who discontinued Na ipodate therapy had undetectable serum TSH concentrations at the time MMI was begun. At the end of the third month of MMI administration, only two patients had detectable serum TSH values, an incidence not different from that observed in the group treated with MMI initially.

Serum AbTPO Antibodies

Elevated levels of AbTPO antibodies (2,295 ± 1,625 U/mL) were present in all patients treated with MMI alone. During MMI therapy, no significant change in AbTPO level (one-way ANOVA) was observed. Serum AbTPO levels (1,922 ± 1,076 U/mL) were elevated in all patients treated with Na ipodate; AbTPO values did not change during Na ipodate administration. Serum AbTPO concentrations were elevated (3,307 ± 2,107 U/mL) before beginning MMI treatment in all patients who discontinued Na ipodate, and they remained elevated throughout the observation period.

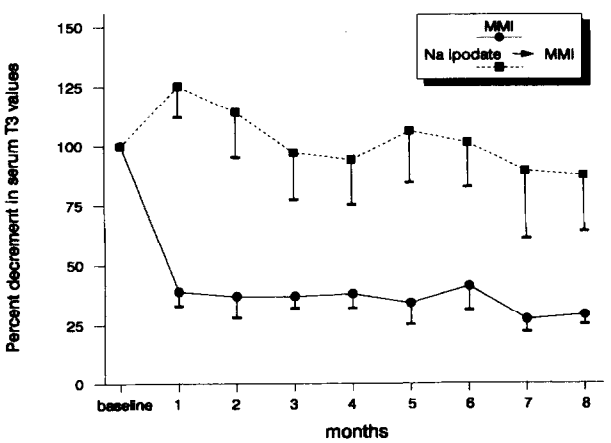

Fig 2. Percent decrease in serum T_3 concentrations in patients treated with MMI alone and in those treated with NA ipodate and then with MMI. The months on treatment represents the time patients received MMI, whether from the beginning or after Na ipodate was withdrawn. The percent decrease was highly significant ($P < .00001$, one-way ANOVA) in patients treated with MMI only, whereas no significant decrease (one-way ANOVA) was observed in patients treated with Na ipodate and then with MMI; bars represent SE.

Heart Rate and Body Weight

The heart rate before treatment with MMI alone was 89 ± 3 beats/min and decreased significantly during the first 3 months of treatment to 74 ± 2 beats/min ($P < .01$, one-way ANOVA). In patients treated with Na ipodate, the basal heart rate was 98 ± 2 beats/min and decreased significantly during the first 3 months of therapy to 82 ± 2 beats/min ($P < .01$, one-way ANOVA).

In patients who discontinued Na ipodate and were then treated with MMI, the heart rate did not continue to decrease, but rather increased to 89 ± 4 beats/min before MMI was given and subsequently decreased significantly to 78 ± 3 beats/min ($P < .01$, one-way ANOVA). Body weight was not significantly different between groups of patients and did not significantly change during treatment.

Thyroid Function After All Therapy Was Discontinued

MMI as sole therapy was discontinued after 12 months; seven patients maintained normal serum T_4 and T_3 concentrations for at least 6 months, and one patient had a recurrence of hyperthyroidism. Two patients were treated with Na ipodate alone for 12 months. One had a recurrence of hyperthyroidism during the next 6 months and was treated with MMI, and the other patient remained euthyroid.

The patients who discontinued Na ipodate were subsequently treated with MMI for different periods of time, but for at least 8 months. After MMI was discontinued, five of nine patients (NS *v* group treated with MMI alone, Fisher's Exact Test) remained euthyroid for at least 6 months.

DISCUSSION

The administration of oral cholecystographic agents to hyperthyroid patients induces a marked decrease in serum T_3 concentrations and a slight decrease in serum T_4 concentrations.[1-3] Furthermore, the decrease in serum T_3 level is more rapid following administration of x-ray contrast agents either alone or with antithyroid drugs than following administration of MMI alone or MMI and stable iodine.[3,9-11] In association with the rapid decrease in serum T_3 concentration, a more rapid amelioration of clinical signs and symptoms of thyrotoxicosis has been observed compared with that in patients treated with antithyroid drugs alone.[3,11]

Oral cholecystographic agents have also been used in the long-term treatment of hyperthyroid patients. In patients with active Graves' disease treated with iopanoic acid for 1 to 12 months, serum thyroid hormone concentrations remained normal in a few, but decreased only temporarily in the majority with a recurrence of hyperthyroidism.[17] In another study, long-term administration (23 to 31 weeks) of

Na ipodate to five hyperthyroid patients decreased serum T_4 and T_3 concentrations to the normal range and significantly decreased heart rate and increased body weight.[13] However, in two patients reevaluated 3 weeks after Na ipodate was withdrawn, serum T_4 and T_3 concentrations increased to values above the normal range. In Graves' hyperthyroidism, treatment for 14 weeks with Na tyropanoate did not normalize serum thyroid hormone concentrations, and the signs and symptoms of thyrotoxicosis often did not abate. Furthermore, levels of thyrotropin receptor antibodies (TRAb) increased slightly during therapy.[15] A single patient with Graves' hyperthyroidism treated with iopanoic acid and propylthiouracil showed a marked decrease in serum total T_3 concentration, whereas serum total and free T_4 and free T_3 concentrations remained markedly elevated and features of thyrotoxicosis persisted.[12] Better results were reported following administration of oral cholecystographic agents in a single patient with severe thyrotoxicosis factitia and in a newborn with neonatal Graves' hyperthyroidism.[14,16] More recently, long-term Na ipodate administration was associated with a high rate of hyperthyroidism during drug therapy and a poor response to subsequent MMI therapy.[19]

In the present study, we have evaluated the effect of long-term administration of Na ipodate on the course of Graves' hyperthyroidism. In the short term (3 months), Na ipodate was effective in reducing serum T_4 and T_3 concentrations and heart rate, thus confirming previous observations.[1-3,9-11] The decrease in serum T_3 concentration and heart rate in patients treated with Na ipodate was similar to that observed in patients treated with MMI alone, whereas the decrease in serum T_4 concentration was greater in patients treated with MMI alone than in those treated with Na ipodate, since the drug decreases T_4 clearance.[4] In previous studies,[1-3,9-11,20,21] the decrease in serum T_4 and T_3 concentrations during the first few days was greater in patients treated with oral cholecystographic agents either alone or in various combinations with other drugs than in those treated with antithyroid drugs alone or with other medications not including the x-ray contrast agents.

We have also observed that in patients treated with Na ipodate and then with MMI, the decrease in serum T_4 and T_3 concentrations was much slower than that observed in patients treated with MMI alone. This finding suggests that the administration of large amounts of iodine to hyperthyroid patients with Graves' disease results in partial resistance to the action of MMI. This observation is in agreement with the recent report by Martino et al[19] and with a single case reported by Caldwell et al[18] describing a patient treated for 10 weeks with 0.5 g Na ipodate and then unsuccessfully with propylthiouracil.

In the present study, patients treated with MMI alone continued to have serum thyroid hormone concentrations in the normal range after 3 months of therapy, whereas eight of 10 patients treated long-term with Na ipodate had an increase in serum T_4 and/or T_3 concentrations above the nadir achieved with Na ipodate alone and an increase in heart rate, requiring withdrawal of the Na ipodate. Thus, only two of 10 patients were appropriately treated over a long term with Na ipodate alone. However, seven of eight patients treated with MMI alone for 12 months were euthyroid and remained so 6 months after MMI was discontinued. This observation confirms previous studies reporting that oral cholecystographic drug therapy for hyperthyroid Graves' disease frequently does not restore and maintain euthyroidism.[13,15,17,19] Furthermore, it has been observed that serum thyroid hormone concentrations may increase to levels even higher than pretreatment values during long-term oral cholecystographic drug therapy[15] or after its withdrawal following long-term or short-term therapy.[9,13]

Patients treated with Na ipodate followed by MMI achieved the same remission rate as those treated with MMI alone. This finding is at variance with the observations of Wartofsky[22] and Solomon et al,[23] who suggested that an increase in iodine intake decreases the remission rate in patients with Graves' disease treated with antithyroid drugs. However, in another study the administration of large amounts of iodide to patients with Graves' hyperthyroidism did not affect the 5-year relapse rate following antithyroid drug therapy.[24]

The thyroid RAIU after 12 months of treatment in the present study did not differ between patients treated with MMI alone and those treated with Na ipodate followed by MMI. This is similar to the observations of Shen et al,[13] who reported that the thyroid RAIU in hyperthyroid patients 7 days after long-term administration of Na ipodate was discontinued was similar to pretreatment values.

We have also measured serum AbTPO levels during the various treatment modalities. No significant decrease in AbTPO levels was observed in patients treated with MMI, Na ipodate, or Na ipodate followed by MMI. It has been observed previously that serum levels of antithyroglobulin and antimicrosomal antibodies did not change in patients treated with iopanoic acid.[17] In contrast, it has been reported that circulating levels of TRAb increased slightly in patients with Graves' disease treated with sodium tyropanoate.[15] In the present study we did not measure TRAb levels, but the fact that Na ipodate treatment had to be discontinued in almost all patients suggests that TRAb were still present.

In conclusion, the present study suggests that long-term Na ipodate treatment of patients with Graves' hyperthyroidism is of little value, since the decrease in serum thyroid hormone concentrations is frequently only temporary. Furthermore, the administration of large amounts of iodide associated with Na ipodate therapy did not adversely affect the remission rate in patients with Graves' disease subsequently treated with antithyroid drugs.

REFERENCES

1. Wu SY, Chopra IJ, Solomon DH, et al: Changes in circulating iodothyronines in euthyroid and hyperthyroid subjects given ipodate (Oragrafin), an agent for oral cholecystography. J Clin Endocrinol Metab 46:691-697, 1978a

2. Wu SY, Chopra IJ, Solomon DH, et al: The effect of repeated administration of ipodate (Oragrafin) in hyperthyroidism. J Clin Endocrinol Metab 47:1358-1362, 1978b

3. Wu SY, Shyh TP, Chopra IJ, et al: Comparison of sodium

ipodate (Oragrafin) and propylthiouracil in early treatment of hyperthyroidism. J Clin Endocrinol Metab 54:630-634, 1982

4. Burgi H, Wimpfheimer CC, Burger A, et al: Changes of circulating thyroxine, triiodothyronine and reverse triiodothyronine after radiographic contrast agents. J Clin Endocrinol Metab 43:1203-1210, 1976

5. Suzuki H, Kadena N, Takenchi K, et al: Effects of three-day oral cholecystography on serum iodothyronines and TSH concentrations: Comparison of the effect among some cholecystographic agents and the effects of iopanoic acid on the pituitary-thyroid axis. Acta Endocrinol (Copenh) 92:477-488, 1979

6. Beng CG, Wellby ML, Symons RG, et al: The effect of ipodate on the serum iodothyronine pattern in normal subjects. Acta Endocrinol (Copenh) 93:175-178, 1980

7. Kleinmann RE, Vagenakis AG, Braverman LE: The effect of iopanoic acid on the regulation of thyrotropin secretion in euthyroid subjects. J Clin Endocrinol Metab 51:339-403, 1980

8. Suzuki H, Noguchi K, Nakahata S, et al: Effects of iopanoic acid on the pituitary-thyroid axis: Time sequence of changes in serum iodothyronines, thyrotropin, and prolactin concentrations and responses to thyroid hormones. J Clin Endocrinol Metab 53:779-783, 1981

9. Roti E, Robuschi G, Manfredi A, et al: Comparative effects of sodium ipodate and iodide on serum thyroid hormone concentrations in patients with Graves' disease. Clin Endocrinol (Oxf) 22:489-496, 1985

10. Robuschi G, Manfredi A, Salvi M, et al: Effect of sodium ipodate and iodide on free T4 (FT4) and free T3 (FT3) concentrations in patients with Graves' disease. J Endocrinol Invest 9:287-291, 1986

11. Roti E, Robuschi G, Gardini E, et al: Comparison of methimazole, methimazole and sodium ipodate, and methimazole and saturated solution of potassium iodide in the early treatment of Graves' disease. Clin Endocrinol (Oxf) 28:305-314, 1988

12. Hamblin PS, Mohr VS, Stockigt JR, et al: Iopanoic acid is of minimal benefit in the treatment of severe hyperthyroidism: Conclusions from a case study. Clin Endocrinol (Oxf) 22:503-510, 1985

13. Shen DC, Wu SY, Chopra IJ, et al: Long term treatment of Graves' hyperthyroidism with sodium ipodate. J Clin Endocrinol Metab 61:723-727, 1985

14. Ermans AM, Bourdoux P: Long-term administration of iopoanoic acid in a case of severe thyrotoxicosis factitia, in Medeiros-Neto G, Gaitan E (eds): Frontiers in Endocrinology. New York, NY, Plenum, 1986, pp 1137-1142

15. Noguchi K, Suzuki H, Nakahata M, et al: Prolonged treatment of hyperthyroidism with sodium tyropanoate, an oral cholecystographic agent: A re-evaluation of its clinical utility. Clin Endocrinol (Oxf) 25:293-301, 1986

16. Karpman BA, Rapoport B, Filetti S, et al: Treatment of neonatal hyperthyroidism due to Graves' disease with sodium ipodate. J Clin Endocrinol Metab 64:119-123, 1987

17. Wang YS, Tsou CT, Lin WH, et al: Long term treatment of Graves' disease with iopanoic acid (Telepaque). J Clin Endocrinol Metab 65:679-682, 1987

18. Caldwell G, Errington M, Toft AD: Resistant hyperthyroidism induced by sodium ipodate used as treatment for Graves' disease. Acta Endocrinol Metab 43:1203-1210, 1989

19. Martino E, Balzano S, Bartalena L, et al: Therapy of Graves' disease with sodium ipodate is associated with a high recurrence rate of hyperthyroidism. J Endocrinol Invest 14:847-851, 1991

20. Sharp B, Reed AW, Tamagna EI, et al: Treatment of hyperthyroidism with sodium ipodate (Oragrafin) in addition to propythiouracil and propanolol. J Clin Endocrinol Metab 53:622-625, 1981

21. Arteaga E, Lopez JM, Rodriguez JA, et al: Effect of the combination of dexamethasone and sodium ipodate on serum thyroid hormones in Graves' disease. Clin Endocrinol (Oxf) 19:619-627, 1983

22. Wartofsky K: Low remission after therapy for Graves' disease: Possible relation of dietary iodine with antithyroid therapy results. JAMA 226:1083-1088, 1973

23. Solomon BL, Evaul JE, Burman KD, et al: Remission rates with antithyroid drug therapy: Continuing influence of iodine intake? Ann Intern Med 107:510-512, 1987

24. Thalassinos NC, Fraser TR: Effect of potassium iodide on relapse-rate of thyrotoxicosis treated with antithyroid drugs. Lancet 2:1983-1984, 1971